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# PERIPHERAL VASCULAR RESPONSE TO ACUTE ANOXIA

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CINCINNATI

The more general reactions of the cardiovascular system of man to the inhalation of oxygen-poor gas mixtures have been described by numerous investigators.[1] They consist of an almost immediate increase in the heart rate, a slight rise in the systolic blood pressure, with no significant change in the diastolic level, and a definite augmentation in the cardiac output. With respect to alterations in the peripheral circulation, the results are not as clearcut. Freeman and his associates [2] studied the rate at which blood flows through the hand during a period of acute anoxia, using the venous occlusion plethysmographic method. They found that either an increase or a decrease of rate was produced. Gellhorn and Steck,[3] utilizing the same procedure and the same vascular bed, also noted apparently inconsistent results, the flow being decreased, unchanged or slightly increased.

Since the circulation through the hand is affected by a variety of vasoconstricting stimuli,[4] it was considered worth while in the present study to investigate the effect of acute anoxia on the flow of blood through the forearm and the leg, as well. Changes noted in these vascular beds are for the most part not complicated by vasomotor effects.

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1. Schneider, E. C., and Truesdell, D.: The Circulatory Responses of Man to Anoxemia, Am. J. Physiol. **71**:90 (Dec.) 1924. Gellhorn, E., and Lambert, E.: The Vasomotor System in Anoxia and Asphyxia, Urbana, Ill., University of Illinois Press, 1939. Graybiel, A.; Missiuro, V.; Dill, D. B., and Edwards, H. T.: Experimentally Induced Asphyxiation in Cardiac Patients, with Especial Reference to Certain Hazards in Air Travel and to the Use of Asphyxiation as a Cardiac Functional Test, J. Aviation Med. **8**:178 (Dec.) 1937.

2. Freeman, N. E.; Shaw, J. L., and Snyder, J. C.: Peripheral Blood Flow in Surgical Shock: Reduction in Circulation Through the Hand Resulting from Pain, Fear, Cold and Asphyxia, with Quantitative Measurements of the Volume Flow of Blood in Clinical Cases of Surgical Shock, J. Clin. Investigation **15**:651 (Nov.) 1936.

3. Gellhorn, E., and Steck, I. E.: Effect of the Inhalation of Gases with a Low Oxygen and Increased Carbon Dioxide Tension on the Peripheral Blood Flow in Man, Am. J. Physiol. **124**:735 (Dec.) 1938.

4. Capps, R. B.: Method for Measuring Tone and Reflex Constriction of Capillaries, Venules and Veins of the Human Hand with Results in Normal and Diseased States, J. Clin. Investigation **15**:229 (March) 1936. Abramson, D. I., and Ferris, E. B., Jr.: Responses of Blood Vessels in the Resting Hand and Forearm to Various Stimuli, Am. Heart J. **19**:541 (May) 1940.

## METHOD

The work was performed on a series of 25 subjects with normal cardiovascular systems. By means of the venous occlusion plethysmographic method, the blood flow in cubic centimeters per minute per hundred cubic centimeters of limb volume was determined separately in the hand, the forearm and the leg; generally two of these sites were studied simultaneously, according to the technic previously described.[5]

The temperature of the water in the plethysmograph was maintained at 32 C., and the room temperature between 25 and 27 C. In order to determine whether the subjects when at rest had blood flow readings which fell within the range of normal, the results obtained in a group of 90 persons previously reported on[6] were utilized as controls.

In each instance the subject inhaled a constant mixture of oxygen and nitrogen in which the concentration of the former gas ranged between 10.5 and 9.4 per cent in the different experiments. The gas mixture was obtained from a spirometer and an auxiliary reservoir, and the exhaled air was automatically discharged into the room through an outlet tube and flutter valve. Special precautions were taken to minimize the dead space in the apparatus and to use a mask which fitted close to the face, so that there was little chance for loss of gas mixture or for introduction of room air into the system.

The usual procedure consisted of taking 15 readings of blood flow after the subject had become accommodated to the environment and was at rest and then applying the mask to the face. A similar number of determinations was made while the subject breathed room air through the mask. Following this, the connection between the mask and the spirometer was opened without the subject's being aware of the change, and a third set of readings was obtained at intervals of one minute during the entire period of relative anoxia; this period lasted from ten to twenty-seven minutes in the different experiments. At the end of it the patient was permitted to breathe room air again, and then, after all readings had returned to normal, the mask was removed from the face; a set of determinations was made in each of these periods. Besides readings of blood flow, the blood pressure, the pulse rate and the respiratory rate were recorded at short intervals during the experiment.

In a number of cases the circulatory response to a period of work was determined, first while the subject breathed room air and then in the middle of the period of anoxia. In each instance this was accomplished in the following manner: A series of readings of blood flow were made with the subject resting, after which the forearm in the plethysmograph was exercised by means of ipsilateral manual compression of a blood pressure bulb connected to an air-filled 5 gallon (19 liter) bottle. The pressure in the system was raised to 30 mm. of mercury by compressing the bulb twenty-five to thirty times in a period of one-half minute. Immediately after the termination of the exercise, readings of blood flow were taken at short intervals (every ten or fifteen seconds) until the flow appeared to return to the previous control level. From these determinations a graph was constructed, and by means of a planimeter the quantity of blood over and beyond the amount which would ordinarily have entered the forearm at rest was obtained.[7] The figure was expressed as cubic centimeters of blood flow repayment per hundred cubic centimeters of limb volume. With this quantity of work, the circulatory response generally lasted no longer than eight minutes. As a result, the exercise could be performed at the end of ten minutes of inhalation of the oxygen-poor gas, at a time when the state of anoxia was fully developed, and still sufficient time would be present for full recovery from the work to take place before the twenty to twenty-five minute period of anoxia was terminated.

## RESULTS

*Hand.*—The vascular responses in the hand were studied in 10 subjects (table 1; chart 1). The control blood flow readings, taken while the patient was at rest, were for the most part smaller than the average of 9.3 cc. per minute per hundred cubic centimeters of limb volume ($\sigma$, 2.1),[8] obtained in another group of normal subjects. This may have been due to the apprehension caused by the anticipation

5. Abramson, D. I.; Zazeela, H., and Marrus, J.: Plethysmographic Studies on Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data, Am. Heart J. **17**:194 (Feb.) 1939. Ferris, E. B., Jr., and Abramson, D. I.: Description of a New Plethysmograph, ibid. **19**:233 (Feb.) 1940.

6. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow and Peripheral Vascular Responses in Hypertensive Subjects, Am. Heart J. **23**:84 (Jan.) 1942.

7. Abramson, D. I., and Fierst, S. M.: The Peripheral Vascular Response to Exercise in the Hyperthyroid State, J. Clin. Investigation **20**:517 (Sept.) 1941.

8. The alpha signifies standard deviation.

of breathing through a mask; in some cases, despite definite attempts to counteract it, this feeling persisted during the rest of the experimental period. The actual application of the mask resulted in a further decrease of blood flow in the hand in 1 subject and a slight increase in 2 others. After the subjects began breathing the oxygen-poor gas mixture, variable results were obtained. In 3 there was a definite progressive decrease in blood flow coincident with the onset of the period of anoxia (chart 1) and in 5 a slight decrease or no change, while in 2 a significant increase was noted. In both of the latter (B. P. and R. B.) the control flow was initially rather low. With readmission of atmospheric air to the system, the circulation remained depressed for at least the following fifteen minutes in 2 subjects, slowly rose in 1, while in 7 it rapidly increased to reach a level considerably higher than

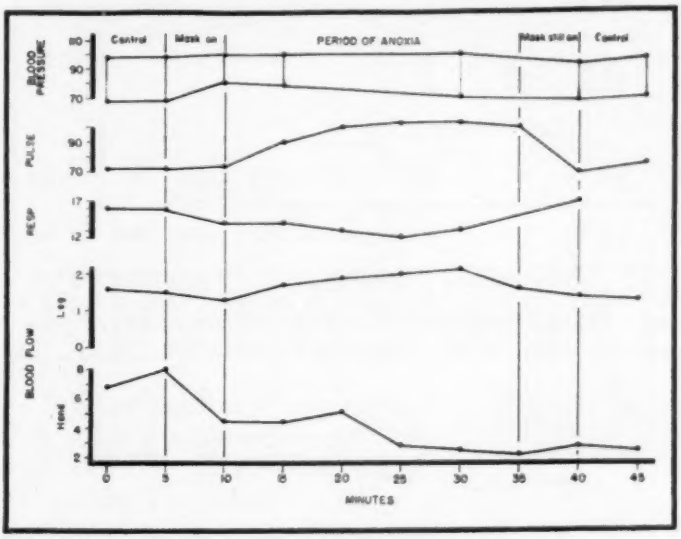


Chart 1.—Effect of relative anoxia on the rate at which blood flowed through the hand and the leg, with the simultaneous effects on the respiratory and pulse rates and the blood pressure.

the control flow. In 2 of the latter group the blood flow then fell after a short interval, while in the remaining 5 it continued elevated for the rest of the experimental period.

*Forearm.*—The vascular responses in the forearm were studied in 10 subjects (table 2; chart 2). The figures for the blood flow at rest were for the most part within the lower range of the average of 1.8 cc. per minute per hundred cubic centimeters of limb volume ($\sigma$, 0.7) for the control series. On application of the mask there was a significant increase in the blood flow in 2 subjects and little change in the others. With the onset of the period of anoxia, the rate of blood flow remained practically unchanged during at least the first five minutes, and then there was a small but definite progressive increase in 6 of the subjects (chart 2), while in 4 no change or even a slight decrease was observed. Two of the latter subjects were rather apprehensive, and previously it had been demonstrated that there was a significant augmentation in blood flow in the forearm merely with the application of the mask (J. B. and M. L.). On readmission of room air there was an almost

TABLE 1.—*Peripheral Vascular Changes in the Hand During a Period of Anoxia*

| Subject | Percentage $O_2$ | Duration of Anoxia, Min. | Blood Flow, Cc. per Min. per 100 Cc. of Limb Vol. | | | | | Pulse Rate per Min. | | | | | Blood Pressure | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control | Mask On | Anoxia | Mask On | Control | Control | Mask On | Anoxia | Mask On | Control | Control | Mask On | Anoxia | Mask On | Control |
| J. S. | 10.1 | 20 | 2.7 | 4.1 | 5 min. 3.2<br>10 min. 3.9<br>15 min. 3.8<br>20 min. 4.7 | 6.1<br>6.3 | 5.6<br>4.6 | 77 | 76 | 5 min. 104<br>10 min. 126<br>15 min. 112<br>20 min. 100 | 80<br>74 | 72<br>76 | 96/70 | 98/70 | 5 min. 110/80<br>10 min. 108/70 | 96/68 | 98/70 |
| H. K. | 10.3 | 27 | 4.3 | 5.4 | 5 min. 3.4<br>10 min. 4.3<br>15 min. 4.8<br>20 min. 1.7<br>25 min. 1.7 | ...<br>1.2 | ... | 65 | 67 | 5 min. 72<br>10 min. 86<br>15 min. 90<br>20 min. 108<br>25 min. 106 | 94 | .. | 98/66 | 98/68 | 5 min. 100/70<br>10 min. 100/68<br>15 min. 106/70<br>20 min. 120/70 | 112/70<br>106/68 | 104/66 |
| B. P. | 10.3 | 25 | 2.5 | 2.0 | 5 min. 2.6<br>10 min. 3.3<br>15 min. 3.3<br>20 min. 6.1<br>25 min. 6.1 | 5.5<br>6.4 | 5.7<br>4.9<br>4.8 | 70 | 68 | 5 min. 96<br>10 min. 80<br>15 min. 100<br>20 min. 96<br>25 min. 100 | 74<br>64<br>64 | 66<br>64 | 100/74 | 102/76 | 5 min. 100/86<br>10 min. 112/88<br>15 min. 116/84<br>20 min. 106/82 | 100/76<br>100/80 | 100/76<br>100/76 |
| R. B. | 10.1 | 20 | 2.3 | 2.8 | 5 min. 2.8<br>10 min. 4.2<br>15 min. 4.7<br>20 min. 5.0 | 5.6<br>9.1 | 4.7<br>6.6 | 102 | 102 | 5 min. 120<br>10 min. 130<br>15 min. 128<br>20 min. 126 | 96<br>96<br>86<br>90 | 96<br>90 | | | | | |
| A. M. | 10.0 | 22 | 7.7 | 4.5 | 5 min. 4.1<br>10 min. 5.1<br>15 min. 2.8<br>20 min. 2.5 | 2.1<br>2.7 | 2.5 | 74 | 73 | 5 min. 81<br>10 min. 90<br>15 min. 102<br>20 min. 100 | 90<br>70<br>72 | 84<br>75 | 98/68 | 96/66 | 5 min. 100/80<br>10 min. 100/78<br>15 min. 100/70 | 94/68 | 100/70<br>96/70 |
| J. L. | 10.0 | 20 | 5.6 | 5.1 | 5 min. 3.4<br>20 min. 1.6 | 1.7<br>1.6 | 4.6 | 78 | 80 | 5 min. 100<br>10 min. 100<br>20 min. 118 | 100<br>81 | 82<br>80 | | | | | |
| D. M. | 10.2 | 20 | 4.5 | 4.6 | 5 min. 3.2<br>20 min. 4.1 | 6.6 | 3.2 | 68 | 68 | 5 min. 75<br>10 min. 90<br>20 min. 110 | 90<br>75<br>60 | 70<br>72 | | | | | |
| I. C. | 10.0 | 10 | 2.8 | 2.8 | 5 min. 1.6<br>10 min. 1.6 | 2.0<br>4.9 | ... | 76 | 68 | 5 min. 94<br>10 min. 99 | 68<br>66 | .. | 102/78 | 104/76 | 5 min. 110/78<br>10 min. 110/78 | 106/80 | 104/78 |
| V. S. | 9.7 | 10 | ... | 7.8 | 5 min. 6.9<br>10 min. 5.8 | 11.2 | ... | 74 | 75 | 5 min. 81<br>10 min. 96 | 84<br>76 | 72<br>74 | ..... | 112/78 | 5 min. 120/74<br>10 min. 122/78 | 120/72<br>116/74 | 108/72<br>110/74 |
| C. V. | 10.0 | 10 | ... | 8.6 | 5 min. 6.4<br>10 min. 6.4 | 9.6<br>9.0 | 10.0 | | | | | | | | | | |

immediate decrease in blood flow in those subjects who had shown an increase, with a return to the control level in five to ten minutes.

*Leg.*—The vascular responses in the leg were studied in 15 subjects (table 3; charts 1 and 3). The control readings all fell within the range of 1.4 cc. per minute

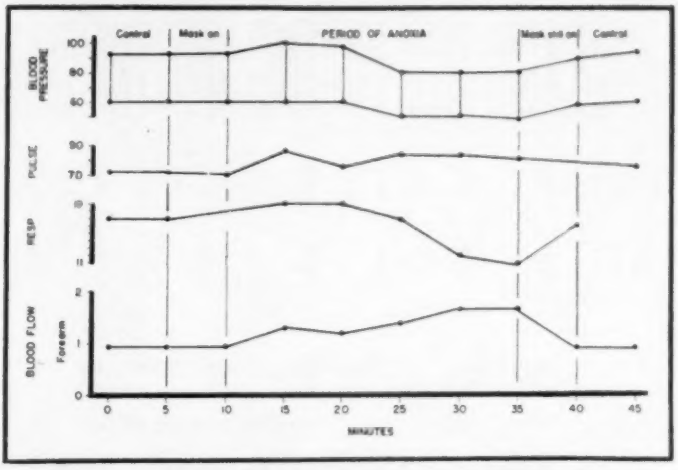


Chart 2.—Effect of relative anoxia on the rate at which blood flowed through the forearm, with the simultaneous effects on the respiratory and pulse rates and the blood pressure.

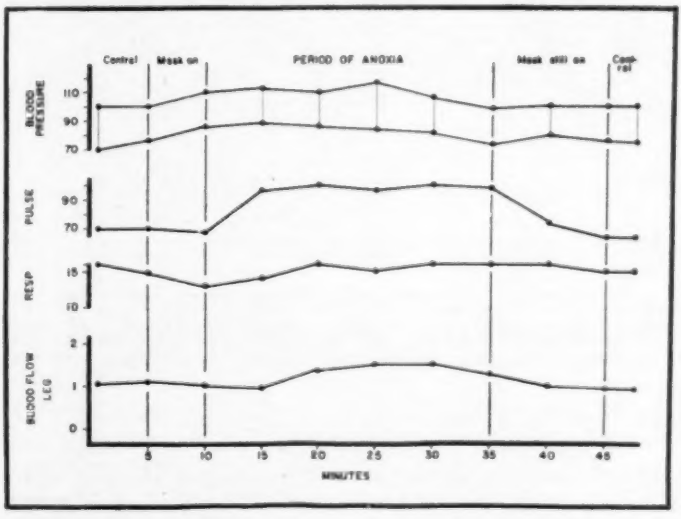


Chart 3.—Effect of relative anoxia on the rate at which blood flowed through the leg, with the simultaneous effects on the respiratory and pulse rates and the blood pressure.

per hundred cubic centimeters of limb volume ($\sigma$, 0.5) for normal subjects. On application of the mask, no significant change took place in the rate of blood flow except in 1 person (M. F.), who was apprehensive and in whom an increase was noted with this procedure. In the first five minutes of the period of anoxia no definite alteration in circulation was observed in any of the subjects (chart 3).

TABLE 2.—*Peripheral Vascular Changes in the Forearm During a Period of Anoxia*

| Subject | Percentage $O_2$ | Duration of Anoxia, Min. | Blood Flow, Cc. per Min. per 100 Cc. of Limb Vol. | | | | | Pulse Rate per Min. | | | | | Blood Pressure | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control | Mask On | Anoxia | Mask On | Control | Control | Mask On | Anoxia | Mask On | Control | Control | Mask On | Anoxia | Mask On | Control |
| J. D. | 10.1 | 20 | ... | 1.0 | 5 min. 1.1<br>10 min. 1.4<br>15 min. 1.3<br>20 min. 1.4 | 1.1<br>1.0 | 1.0 | 86 | 86 | 5 min. 106<br>10 min. 110<br>15 min. 106<br>20 min. 98 | 88 | .. | 96/74 | 96/74 | 5 min. 104/76<br>10 min. 104/72<br>15 min. 104/74<br>20 min. 94/64 | 98/76 | 96/72 |
| E. H. | 10.1 | 25 | 0.9 | 0.9 | 5 min. 1.3<br>10 min. 1.2<br>15 min. 1.4<br>20 min. 1.7<br>25 min. 1.7 | 1.3<br>1.3<br>1.0 | 1.3<br>1.0 | 72 | 70 | 5 min. 87<br>10 min. 92<br>15 min. 84<br>20 min. 84<br>25 min. 82 | 75<br>70<br>75 | 72<br>75<br>72 | 94/64 | 92/60 | 5 min. 100/60<br>10 min. 94/50<br>15 min. 80/50<br>20 min. 80/50<br>25 min. 80/48 | 90/58<br>88/58 | 94/60<br>92/60 |
| C. W. | 10.4 | 25 | 0.6 | 0.5 | 10 min. 0.6<br>15 min. 0.6<br>20 min. 0.9<br>25 min. 0.9 | 0.8<br>0.5 | 0.5<br>0.6 | 71 | 74 | 5 min. 92<br>10 min. 104<br>15 min. 108<br>20 min. 112<br>25 min. 106 | 78<br>70<br>70 | 76<br>70 | 96/46 | 100/50 | 5 min. 106/46<br>10 min. 104/40<br>15 min. 108/40<br>20 min. 96/46<br>25 min. 98/44 | 100/48<br>96/50 | 96/52<br>102/54 |
| R. B. | 10.1 | 20 | 0.9 | 0.8 | 5 min. 0.8<br>10 min. 0.8<br>15 min. 1.0<br>20 min. 0.8 | 0.7<br>0.8 | 0.7<br>0.6 | 76 | 78 | 5 min. 105<br>10 min. 104<br>15 min. 106 | 96<br>90<br>82 | 72<br>70<br>70 | 104/58 | 106/58 | 5 min. 112/62<br>10 min. 110/64<br>15 min. 112/60 | 112/62<br>108/60 | 106/58<br>102/58 |
| J. B. | 10.1 | 25 | 1.8 | 2.7 | 5 min. 2.9<br>10 min. 1.8<br>15 min. 1.6<br>20 min. 2.1<br>25 min. 2.2 | 2.1<br>1.6 | 2.0<br>1.7 | 80 | 94 | 5 min. 118<br>10 min. 126<br>15 min. 130<br>20 min. 124<br>25 min. 126 | 126<br>108<br>118 | 108<br>104<br>105 | 110/76 | 118/80 | 5 min. 126/84<br>10 min. 126/86<br>15 min. 120/82<br>20 min. 120/72<br>25 min. 118/78 | 118/84 | 116/78 |
| S. H. | 10.2 | 25 | 1.1 | 1.3 | 5 min. 1.3<br>10 min. 1.1<br>15 min. 1.1<br>20 min. 1.1<br>25 min. 1.2 | 1.1<br>1.2 | 1.0 | 78 | 76 | 5 min. 87<br>10 min. 87<br>15 min. 83<br>20 min. 82<br>25 min. 80 | 82<br>72<br>68 | 66<br>70 | 120/78 | 118/80 | 5 min. 120/80<br>10 min. 116/78<br>15 min. 120/80<br>20 min. 116/80 | 120/78<br>116/78 | 116/80<br>116/80 |
| M. L. | 10.1 | 15 | 1.7 | 2.8 | 5 min. 2.7<br>15 min. 2.7 | 2.4 | 1.8 | 96 | 96 | 5 min. 97<br>10 min. 110<br>15 min. 107 | 85<br>84 | 86 | 130/76 | 130/70 | 5 min. 130/72<br>10 min. 138/60 | 130/72<br>132/80 | 126/70 |
| K. F. | 10.1 | 20 | 2.7 | 2.3 | 5 min. 3.3<br>20 min. 3.0 | 2.7 | 2.6 | .. | 75 | 5 min. 88<br>10 min. 90<br>15 min. 90 | 68 | 73 | | | | | |
| J. L.* | 10.0 | 20 | 1.0 | 0.9 | 5 min. 0.9<br>20 min. 1.3 | 1.0<br>0.9 | 1.1 | | | | | | | | | | |
| D. M.* | 10.2 | 20 | 1.4 | 1.2 | 5 min. 1.4<br>20 min. 2.0 | 1.6 | 1.1 | | | | | | | | | | |

* The changes in pulse rate recorded for these subjects are included in table 1.

* The changes in pulse rate recorded for these subjects are included in table 1.

| Subject | Percentage $O_2$ | Duration of Anoxia, Min. | Blood Flow, Cc. per Min. per 100 Cc. of Limb Vol. | | | | | Pulse Rate per Min. | | | | | Blood Pressure | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control | Mask On | Anoxia | Mask On | Control | Control | Mask On | Anoxia | Mask On | Control | Control | Mask On | Anoxia | Mask On | Control |
| J. H. | 10.2 | 20 | 1.0 | 1.2 | 5 min. 1.2<br>10 min. 1.4<br>15 min. 1.4<br>20 min. 1.4 | 1.0 | 1.1 | 74 | 78 | 5 min. 82<br>10 min. 88<br>15 min. 86 | 58<br>62 | 69 | 112/68 | 116/82 | 5 min. 116/76<br>15 min. 114/78 | 104/72<br>110/72 | 114/76 |
| H. S. | 9.8 | 20 | 1.2 | 1.1 | 5 min. 1.1<br>10 min. 1.2<br>15 min. 1.3<br>20 min. 1.4 | 1.2<br>1.2 | 1.1 | 84 | 84 | 5 min. 90<br>10 min. 102<br>15 min. 118<br>20 min. 112 | 86 | 84 | 106/72 | 110/72 | 5 min. 106/76<br>10 min. 108/72<br>15 min. 106/72 | 106/76 | 106/76 |
| M. A. | 10.0 | 20 | 1.4 | 1.1 | 5 min. 1.3<br>10 min. 1.3<br>15 min. 1.5<br>20 min. 1.6 | 1.4 | 1.5 | 76 | 72 | 5 min. 84<br>10 min. 100<br>15 min. 100<br>20 min. 100 | 68<br>68 | 68 | 118/72 | 122/72 | 5 min. 122/72<br>10 min. 124/72<br>15 min. 126/70<br>20 min. 124/70 | | |
| E. N. | 9.4 | 15 | 1.1 | 1.4 | 5 min. 1.5<br>10 min. 1.7<br>15 min. 2.0 | 1.7<br>1.6 | 1.3<br>1.4 | 76 | 81 | 5 min. 108<br>10 min. 102<br>15 min. 92 | 84<br>76 | 72<br>68 | 112/68 | 114/70 | 5 min. 116/70<br>10 min. 112/70<br>15 min. 114/68 | 110/68 | 108/68 |
| J. K. | 10.5 | 15 | 1.3 | 1.6 | 5 min. 1.4<br>10 min. 1.3<br>15 min. 1.4 | 1.2 | ... | 77 | 76 | 5 min. 84<br>10 min. 90<br>15 min. 86 | 69<br>69 | 72 | 104/70 | 108/72 | 5 min. 110/70<br>10 min. 108/70<br>15 min. 108/70 | 108/62 | |
| M. F. | 10.1 | 20 | 1.3 | 2.0 | 5 min. 2.4<br>10 min. 1.9<br>15 min. 2.1<br>20 min. 2.1 | 1.6<br>1.3<br>1.4 | 1.3<br>1.0 | 86 | 95 | 5 min. 122<br>10 min. 116<br>15 min. 124<br>20 min. 114 | 105<br>82<br>88 | 90<br>86 | 120/74 | 130/82 | 5 min. 130/90<br>10 min. 125/84<br>15 min. 120/74<br>20 min. 114/70 | 110/70<br>110/80 | 110/80<br>110/80 |
| G. E. | 10.2 | 20 | 1.7 | 1.8 | 5 min. 2.1<br>10 min. 2.1<br>15 min. 2.6<br>20 min. 2.8 | 2.0<br>1.6 | 1.5<br>1.3 | 80 | 77 | 5 min. 92<br>10 min. 94<br>15 min. 98<br>20 min. 92 | 72<br>78 | 76<br>78 | 118/74 | 118/80 | 5 min. 120/84<br>10 min. 120/84<br>15 min. 118/80<br>20 min. 118/78 | 116/74<br>112/78 | 118/84<br>120/80 |
| J. S.* | 10.1 | 20 | 1.1 | 1.4 | 5 min. 1.3<br>10 min. 1.8<br>15 min. 1.8<br>20 min. 1.5 | 1.3<br>1.2<br>1.3 | 1.1 | | | | | | | | | | |
| C. V.* | 10.0 | 10.0 | 1.2 | 1.2 | 5 min. 1.5<br>10 min. 1.6 | 1.7<br>1.0 | 1.0 | | | | | | | | | | |
| V. S.* | 9.7 | 10.0 | ... | 2.0 | 5 min. 2.3<br>10 min. 2.2 | 2.0<br>1.7 | | | | | | | | | | | |
| I. C.* | 10.0 | 10.0 | ... | 0.9 | 5 min. 1.0<br>10 min. 1.3 | 1.0<br>0.9 | | | | | | | | | | | |
| R. B.* | 10.1 | 20.0 | 1.5 | 1.5 | 5 min. 1.5<br>10 min. 2.2<br>15 min. 2.4<br>20 min. 2.9 | 1.9<br>2.0 | 1.5<br>1.7 | | | | | | | | | | |
| B. P.* | 10.3 | 25 | 1.1 | 1.0 | 5 min. 0.9<br>10 min. 1.3<br>15 min. 1.4<br>20 min. 1.5<br>25 min. 1.2 | 1.0<br>0.9 | 0.9<br>1.3<br>1.3 | | | | | | | | | | |
| H. K.* | 10.3 | 27 | 0.7 | 1.0 | 5 min. 1.0<br>10 min. 1.1<br>15 min. 1.1<br>20 min. 0.8<br>25 min. 1.0 | 1.0 | 0.9 | | | | | | | | | | |
| A. M.* | 10.0 | 22 | 1.6 | 1.3 | 5 min. 1.7<br>10 min. 1.9<br>15 min. 2.0<br>20 min. 2.1 | 1.6<br>1.4 | 1.3 | | | | | | | | | | |

* The changes in pulse rate and blood pressure recorded for these subjects are included in table 1.

Then, in 11, the rate of blood flow began to increase, and the augmented circulation was maintained during the remainder of the period; with readmission of room air into the system, the flow quickly returned to the previous control level (charts 1 and 3). In 4 of the subjects, no real alteration in circulation through the leg was noted during or after the anoxic period. These findings to some extent are similar to those of Lennox and Gibbs,[9] who studied changes in arteriovenous oxygen differences in blood from the leg following inhalation of oxygen-poor gases. They found that pronounced anoxia resulted in an increased flow in this vascular bed, while with a milder form a decrease was noted, the latter observation being difficult to explain, according to these investigators.

With respect to the other determinations, it was found that in every instance the pulse rate began to rise almost immediately after the onset of the period of anoxia (charts 1, 2 and 3), the maximal average acceleration for the group being 27 beats per minute. As soon as this period was terminated, the pulse rate quickly fell, in some instances temporarily reaching a lower level than that observed at the beginning of the experiment. The effect on blood pressure was much less marked (charts 1, 2 and 3). In 5 instances no change in the systolic level took place, while in the remaining 16 cases there was an average rise of 6 mm. of mercury. The

TABLE 4.—*Peripheral Vascular Response to Exercise During Anoxia* *

| | Control Period | | | | Period of Anoxia | | | |
|---|---|---|---|---|---|---|---|---|
| Subject | Total Blood Flow Repayment,† Cc. | Maximal Single Response, Cc. per Min. per 100 Cc. of Limb Vol. | Time of Maximal Response, Sec. | Duration of Recovery Period, Min. | Total Blood Flow Repayment, Cc. | Maximal Single Response, Cc. per Min. per 100 Cc. of Limb Vol. | Time of Maximal Response, Sec. | Duration of Recovery Period, Min. |
| J. L. ..... | 10.1 | 7.2 | 15 | 8 | 15.7 | 7.1 | 25 | 9 |
| K. F. ..... | 12.2 | 8.2 | 20 | 6 | 13.5 | 9.7 | 20 | 6.5 |
| D. M. ..... | 16.9 | 9.1 | 20 | 7.5 | 19.6 | 13.5 | 30 | 9.0 |

* The pressure in a 5 gallon bottle was raised to 30 mm. of mercury in each instance by the subject's compressing a blood pressure bulb twenty-seven to thirty times in approximately one-half minute.

† This means the excess quantity of blood for each 100 cc. of limb volume entering the extremity during the period of recovery.

diastolic level, for the most part, varied insignificantly. The respiratory rate either increased or decreased somewhat (charts 1, 2 and 3), the respiratory movements generally being of somewhat greater amplitude in the latter part of the anoxic period. Except for occasional complaints of light-headedness and headache and some cyanosis of the face and hands, the subjects experienced no untoward effects from the inhalation of the oxygen-poor gas mixture.

*Circulatory Response to Exercise.*—In the 3 subjects in whom the response to a definite quantity of exercise in the anoxic state was studied, the blood flow repayment was either somewhat or definitely greater than that obtained in the control period (table 4). Further, the first few readings obtained immediately after the exercise was terminated revealed that the blood flow generally rose to a higher level than was observed during the control period. The period of recovery was also a little longer.

## COMMENT

It is obvious that the response of the blood vessels of the hand to acute general anoxia is variable, our findings in this respect being similar to those of Freeman and his associates [2] and of Gellhorn and Steck.[3] In contrast, the

9. Lennox, W. G., and Gibbs, E. L.: Blood Flow in the Brain and the Leg of Man, and the Changes Induced by Alteration of Blood Gases, J. Clin. Investigation **11**:1155 (Nov.) 1932.

observation of Freeman and his co-workers that there is a uniform increase in flow through the sympathectomized hand under these circumstances suggests that the different types of reactions normally elicited are in some way related to the presence of vasoconstrictor nervous impulses. According to Gellhorn and Steck, the variability in the results is due to the fact that the increased vasoconstrictor tonus resulting from the stimulation of the vasomotor center competes with the local dilatory effect of the different metabolites formed in the presence of oxygen deficiency, the rate of blood flow being determined by which of the two factors predominates. We also feel, however, that the element of apprehension associated with the procedure, even in the case of trained subjects, plays an important role in this respect. Another possibility which may contribute to the vasoconstriction in this site is the increase in the depth of respiration frequently noted in the latter portion of the anoxic state, for a deep breath by itself has been shown to produce a marked decrease in blood flow through the fingers.[10] Because of all these complicating factors, the responses of the vessels in the hand to a lack of oxygen cannot be considered to be representative of peripheral blood flow and hence should not be given much significance as far as general responses are concerned.

With respect to the results in the forearm and the leg, it can be stated that in the majority of the cases a small but definite and progressive increase in peripheral blood flow was observed during the period of relative anoxia. Of interest in this respect are the findings of Grollman,[11] who investigated the circulatory effect of a series of oxygen and nitrogen mixtures. He noted that no change in cardiac output took place until the oxygen had fallen to 11.6 per cent; when the concentration dropped below this point, the readings for the minute volume output rose rapidly. These findings have since been confirmed by a number of investigators.[12] It is quite possible, therefore, that since approximately a 10 per cent oxygen mixture was used in the present study, the increase in blood flow in the forearm and the leg resulted in part, at least, from an augmented cardiac output elicited by the lack of oxygen. Further, the alteration in circulation may also have been due to the local vasodilatory effect of want of oxygen on the vessels themselves. A complicating consideration is the fact that under the influence of anoxia the respiratory minute volume increases and consequently carbon dioxide will be blown off in greater than normal amounts, this in turn resulting in a state of acapnia. It is possible that under such circumstances there might be a decrease in venous return to the heart due to a reduction in the tonus of striated muscle as well as in the tone of the vasomotor center; this would eventually manifest itself in the form of diminished peripheral circulation. However, since the opposite response was observed, it can be inferred either that this factor did not play an important role in altering the blood flow under the present experimental conditions or that the increased cardiac output elicited by the anoxia more than compensated for any decrease that might have resulted from the acapnia alone.

The finding that the pulse rate increased almost at once while the changes in blood flow were first noted five to ten minutes after the onset of anoxia suggests

10. Mulinos, M. G., and Shulman, I.: The Effects of Cigarette Smoking and Deep Breathing on the Peripheral Vascular System Studied by Five Methods, Am. J. M. Sc. **199**:708 (May) 1940.

11. Grollman, A.: Physiological Variations of Cardiac Output in Man: The Effect of High Altitude on Cardiac Output and Its Related Functions; Account of Experiments Conducted on Summit of Pike's Peak, Colorado, Am. J. Physiol. **93**:19 (May) 1930.

12. (*a*) Asmussen, E., and Chiodi, H.: The Effect of Hypoxemia on Ventilation and Circulation in Man, Am. J. Physiol. **132**:426 (March) 1941. (*b*) Wiggers, C. J.: Cardiac Adaptions in Acute Progressive Anoxia, Ann. Int. Med. **14**:1237 (Jan.) 1941.

that there was no causal relation between these two factors. Further, it does not seem as though the alteration in pulse rate was dependent on want of oxygen in the tissues, since it appeared much before this state could have been reached. The change can more likely be explained on the basis of central stimulation resulting in increased accelerator nerve activity and decreased vagal tone.[12b] Finally, the observation of Schmidt and Comroe [13] that in animals low oxygen tension produces acceleration of pulse only in the presence of intact chemoreceptors of the carotid body may also apply to this condition in man.

The fact that a greater than 50 per cent decrease in oxygen content (from 20.9 per cent in air to 10 per cent in the mixture) produced only a moderate change in peripheral blood flow is readily understandable if one considers that in the normal subject under resting conditions only a small proportion of the total quantity of oxygen in the arterial blood is removed in passage through the vessels of muscles. It would be expected, therefore, that during anoxia of the degree utilized in the present study there would be no necessity for a marked increase in the rate of peripheral blood flow in order to satisfy the oxygen requirements of the resting tissues.

The findings with exercise are in accord with the aforementioned view. As previously reported,[7] the magnitude of the postexercise blood flow repayment is an indication of the efficiency of the compensatory mechanisms elicited during the period of work and also of the metabolism of the tissues involved. In other words, the performance of a specific amount of work requires the expenditure of a certain amount of energy, the latter being restored through the nutritive materials in the blood stream. In order to effect this, there is a local increase in the blood flowing through the tissues both during the actual work and in the postexercise period. On the basis that the metabolism of the tissues does not change significantly during a short period of relative anoxia, our findings with exercise assume some significance. The fact that a greater postexercise blood flow repayment was elicited in the case of the work performed under want of oxygen indicates that the compensatory mechanisms functioning during the exercise were not as adequate as under normal conditions, and hence a greater portion of the blood flow debt had to be repaid subsequently. Since one of the adjustments called forth by exercise is an increase in the utilization of arterial oxygen, it can readily be seen that during want of oxygen the quantity of this gas obtained in this manner might not be as great as under ordinary conditions. Therefore, the increased amount of oxygen required during work would have to be satisfied by a greater than normal augmentation in the rate of peripheral blood flow.

## SUMMARY AND CONCLUSION

The effect on the peripheral circulation of a period of relative anoxia was studied in a series of 25 normal subjects by the venous occlusion plethysmographic method. The inhalation of an oxygen-poor gas mixture (approximately 10 per cent oxygen and 90 per cent nitrogen) for periods of from ten to twenty-seven minutes produced a small but definite increase in the rate at which blood flowed through the forearm and the leg in the majority of subjects and generally a decrease in the circulation in the hand. In view of the fact that the vessels in the hand respond to all types of vasoconstricting stimuli, the results obtained during the period of anoxia were not given much general significance.

13. Schmidt, C. F., and Comroe, J. H., Jr.: Functions of Carotid and Aortic Bodies, Physiol. Rev. **20**:115 (Jan.) 1940.

Associated with the increase in the blood circulating through the forearm and the leg were a significant augmentation in pulse rate, a slight elevation of systolic blood pressure and variable changes in the rate of respiration.

The circulatory response to a period of exercise during the inhalation of the oxygen-poor gas was compared with that obtained under normal circumstances. The results were interpreted to indicate that the compensatory adjustments to work in a state of relative anoxia were not as adequate as those elicited normally.

The possible mechanisms responsible for the circulatory changes present during a period of anoxia are discussed.

Dr. Kamillo Flachs and Dr. Sidney M. Fierst cooperated in this study, and Mrs. Robert Senior and Mrs. William Littleford gave valuable technical assistance.

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# HEMORRHAGIC LESIONS OF THE CORONARY ARTERIES

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Several types of acute occlusion of the coronary arteries have been described.[1] Interpretation of the pathologic changes associated with the more familiar form, usually accompanied by arterial thrombosis, has not resulted in a clear understanding of the basic factors involved. In recent years more emphasis has been accorded to the hemorrhage in the intimal and subintimal layers of the occluded arteries, and several authors have attached great importance to this phenomenon in the mechanism of coronary occlusion.[2] This has resulted partly from a relatively new interpretation of the origin and significance of hemorrhage in the walls of small arteries.[3] It had generally been considered that extravasated blood in this location either was derived from the lumen of the artery or occurred as a result of inflammatory exudation.[4] Lately it has been demonstrated that in most instances intramural hemorrhage of the coronary artery arises from the vascular channels of the intima, these being especially numerous in the neighborhood of atheromatous plaques.[5] According to the recent theories, which deal with the relation of subintimal hemorrhages to acute occlusion of the coronary artery, bleeding from these tiny channels causes arterial occlusion either directly by pressure of the resulting hematoma [2d] or indirectly by precipitation of a thrombus near the site of the hemorrhage. Among the factors acting to produce such hemorrhages, it has been proposed that fluctuations in blood pressure play an important part.[2c]

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1. (*a*) Benson, R. L.: The Present Status of Coronary Arterial Disease, Arch. Path. **2**:876-916 (Dec.) 1926. (*b*) Faulkner, J. M.; Marble, H. C., and White, P. D.: The Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, J. A. M. A. **83**:2080-2082 (Dec. 27) 1924. (*c*) Hamman, L.: The Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**:273-319 (April) 1926.

2. (*a*) Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, Arch. Path. **22**:313-324 (Sept.) 1936; (*b*) Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, ibid. **25**:474-487 (April) 1938; (*c*) Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi, Canad. M. A. J. **44**:114-120 (Feb.) 1941. (*d*) Wartman, W. B.: Occlusion of the Coronary Arteries by Hemorrhage into Their Walls, Am. Heart J. **15**:459-470 (April) 1938. (*e*) Horn, H., and Finkelstein, L. E.: Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion, ibid. **19**:655-682 (June) 1940.

3. Winternitz, M. C.; Thomas, R. M., and LeCompte, P. M.: Studies in the Pathology of Vascular Disease, Am. Heart J. **14**:399-404 (Oct.) 1937. Nelson, M. G.: Intimal Coronary Artery Haemorrhage as a Factor in the Causation of Coronary Occlusion, J. Path. & Bact. **53**:105-116 (July) 1941. Paterson (footnote 2 *a*, *b* and *c*).

4. (*a*) Leary, T.: Vascularization of Atherosclerotic Lesions, Am. Heart J. **16**:549-554 (Nov.) 1938. (*b*) Boyd, A. N.: An Inflammatory Basis for Coronary Thrombosis, Am. J. Path. **4**:159-166 (March) 1928. Benson.[1a]

5. Leary, T.: Atherosclerosis: Special Consideration of Aortic Lesions, Arch. Path. **21**: 419-458 (April) 1936. Paterson (footnote 2 *a*, *b* and *c*). Horn and Finkelstein.[2e] Leary.[4a]

## MATERIAL STUDIED

The coronary arteries of 135 selected hearts were carefully studied. Ninety per cent of the patients had been more than 40 years of age at the time of death. Standard procedures of examination were carried out. In addition, a special method of treating arteries which were suspected of being involved by recently occluding lesions was employed. These arteries were dissected intact from the hearts, fixed, dehydrated in alcohol and finally cleared in pure benzene as a preliminary step to the cutting of segments for embedding in paraffin. This procedure facilitated the location of proper sites for sectioning without distortion of the tissue, which is rendered friable by hemorrhagic lesions. Intimal hemorrhage was observed in 54 of the 135 cases (40 per cent). The hemorrhagic lesions[6] ranged from 2 or 3 mm. in diameter to massive processes which extended several centimeters along the course of an artery and caused collapse of the intima and resultant obliteration of the lumen.

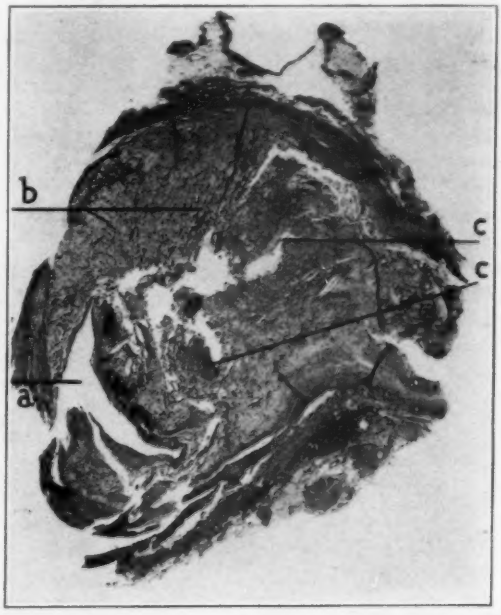


Fig. 1.—The lumen, *a*, of this coronary artery has been almost obliterated by an intimal process which consists of large lipoid-containing cells, elements of organization and hemorrhage. Many young capillaries are present among the lipoid-containing cells, *b*, and there are a few scattered lymphocytes. Hemorrhage, *c*, is relatively minimal. There was no coronary thrombus, although the patient died during a severe attack of angina pectoris. Changes indicative of recent myocardial infarction were not observed (× 14).

Among the individual arteries examined were 20 in which recent occlusion was found, and in at least 9 of these the occlusion had been directly produced by hemorrhagic arterial lesions. Similar lesions were present in the other 11 occluded arteries, but associated arterial thrombi were considered the direct cause of occlusion. Many organized hemorrhagic lesions were observed, particularly in arteries in cases in which healed or chronic myocardial infarcts were found. That these lesions had contained extravasated blood was determined by the presence of phagocytosed iron pigment.

6. The term "hemorrhagic lesion" is used in preference to "intimal hemorrhage" to avoid the assumption that hemorrhage is the cause of arterial occlusion.

MICROSCOPIC FEATURES OF HEMORRHAGIC ARTERIAL LESIONS

Wherever hemorrhage was encountered in the intima of a coronary artery, coexistent degenerative changes were to be found which in most cases denoted an active pathologic process. The involved portion of intima was thickened, and

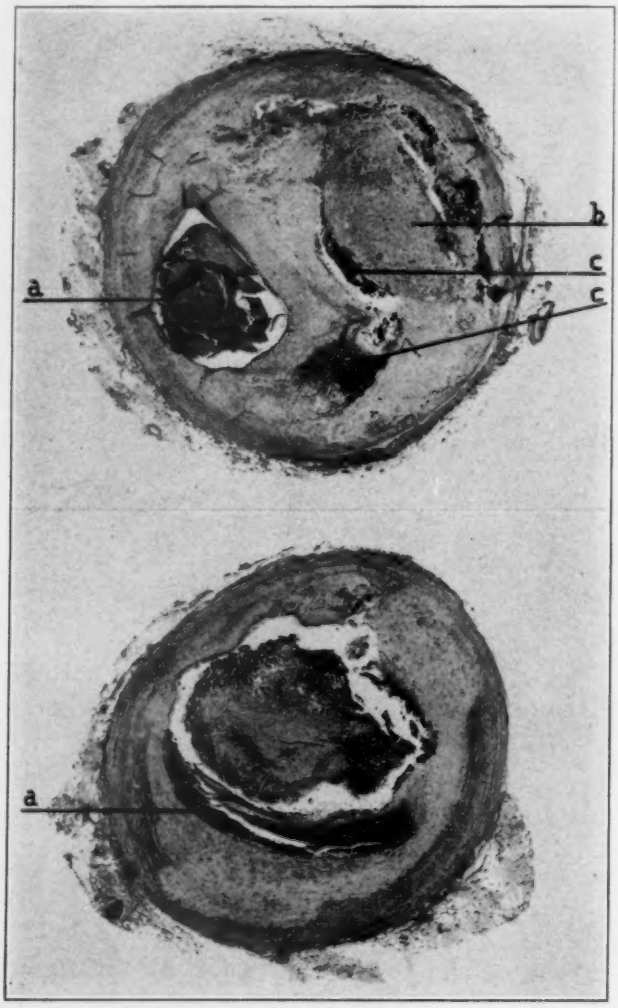


Fig. 2.—Upper and lower: Two levels of a coronary artery involved throughout almost its entire course by a hemorrhagic process. The lumen, *a*, which was obliterated at some levels, was filled with either a late antemortem or a postmortem thrombus. Most cellular elements had been destroyed, but large blotches of lipoid substance, *b*, probably represent residua of lipoid-containing cells. In isolated areas the lesion is stained with hemorrhage, *c*.

the planes of tissue were separated, distorted and generally displaced toward the lumen of the artery. The interstices of the intimal connective tissue contained such

elements as large lipophages or their granular remnants, lymphocytes, fibroblasts chains of endothelial cells and hemorrhage in various stages of dissolution and absorption. Cholesterol crystals were not so prevalent in these as in older lesions. Essentially the same picture was to be found at other levels of an involved artery, in varying

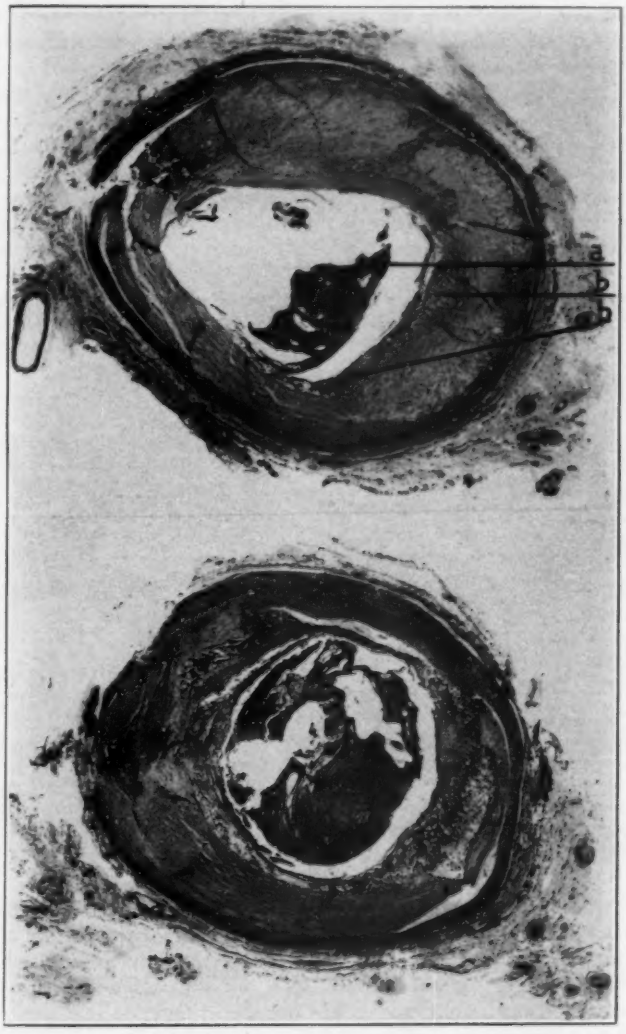


Fig. 3.—Two levels of a coronary artery illustrating the relationship of a thrombus to a hemorrhagic arterial lesion. Upper: The section was made near the head of the thrombus, *a*, which was originally adherent to the arterial wall and overlay the intimal change, *b*. Lower: At the lower level the intimal change is more advanced.

degrees of advancement, sometimes with little, if any, accompanying hemorrhage. At no point did the quantity of extravasated blood seem commensurate with the size of the lesion as a whole. In fact, a few large, occluding lesions were observed

which, although accompanied by a relatively small amount of hemorrhage, were nevertheless the only apparent cause of acute myocardial infarction in some cases or of sudden death during attacks of angina pectoris in others. Such lesions retained their cellular configuration more completely, but were altered by varying degrees of early organization.

It did not seem logical from any standpoint to assume that hemorrhage was the primary factor in the production of these occluding lesions. Any expanding intimal process, whatever its nature, of necessity develops a pressure equal to or greater than that of the blood within the arterial lumen. The pressure of blood within the coronary arteries in all probability surpasses that within microscopic intimal blood channels, even though some or all of them should arise from the arterial lumen itself. It also seems probable that the quantity of extravasated blood in the lesions observed was a measure of the number of capillaries and vascular spaces disrupted by the primary pathologic condition, their contents diffusing into neighboring portions of the intima but not bleeding actively into it.

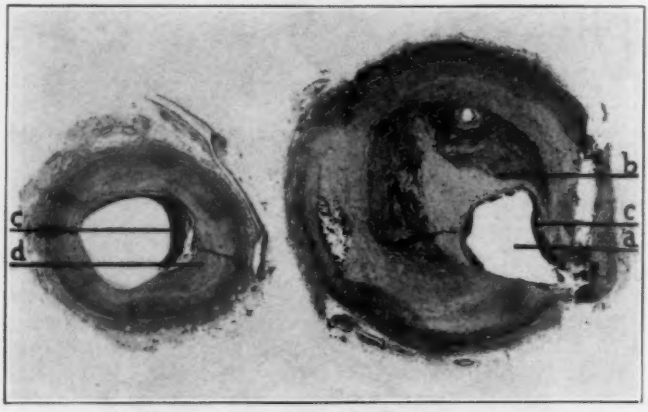


Fig. 4.—The lumen, *a*, of this coronary artery was displaced and obliterated (at a lower level) by a hemorrhagic intimal process, *b*, consisting of fibrillar intimal change, hemorrhage, elements of organization and lymphocytic proliferation. Mural thrombosis is present in the main artery as well as in its adjacent branch, *c*. In the latter, *d*, however, the intimal change has not become hemorrhagic, although in other respects it was similar. The pathologic change began well away from the lumen, separated from it by normal intimal tissue. An acute myocardial infarct resulted from this lesion.

Arterial thrombi when present were invariably associated with hemorrhagic lesions. In each instance of an arterial thrombus, examination of the arterial wall along its course revealed the type of intimal change that has been described, accompanied by hemorrhage. Mural thrombi were usually attached to the endothelial surface overlying these lesions, and it was noted with interest that they overlay the lesions in their entirety and were not confined to areas of hemorrhage; this finding further substantiates the conception that hemorrhage in itself is not the most significant factor in the pathologic condition represented.

The three general groups of recent hemorrhagic arterial lesions encountered were: (1) those in which hemorrhage was related to the presence of numerous lipoid-containing cells, (2) those characterized by hemorrhage in association with proliferative intimal changes and (3) those in which small hemorrhages were adjacent to calcified plaques.

Lesions of the first group (figs. 1, 2 and 3) were encountered most frequently, attained the greatest size and were the pathologic finding in all but 2 of the 9 instances in which acute coronary occlusion had been produced directly by hemorrhagic arterial lesions. The largest lesions extended along the greater portion of the artery, replaced its lumen and in consistency and gross appearance somewhat

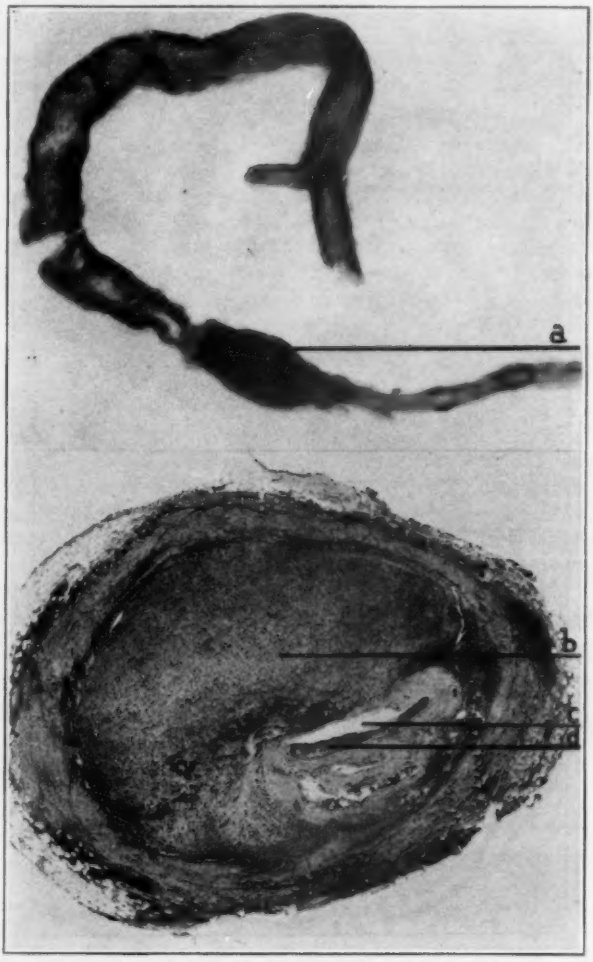


Fig. 5.—An unusual type of hemorrhagic lesion. Upper: Gross appearance of the hemorrhagic lesion, *a*, as brought out by a clearing method. Lower: Microscopic appearance; the lesion, *b*, consisted of hemorrhage, lymphocytes, endothelial cells, phagocytosed as blood pigment and young capillaries. The reduced lumen, *c*, partially obstructed by a mural thrombus, *d*, may be noted. The heart in this case was involved by an acute myocardial infarct.

resembled recent thrombi. Sections of these lesions were observed microscopically to consist principally of large lipoid-containing cells or their granular remnants. The latter, which were composed of lipoid globules, frequently retained the general

outline of the cells. Extravasated blood was invariably present. If the compressed arterial lumen was not obliterated, it either remained patent or was obstructed by a thrombus.

A few of the lesions of this group in which cellular configuration was only slightly altered were considered as representing less active processes. In these such organization as was present was early and minimal, and much of it was

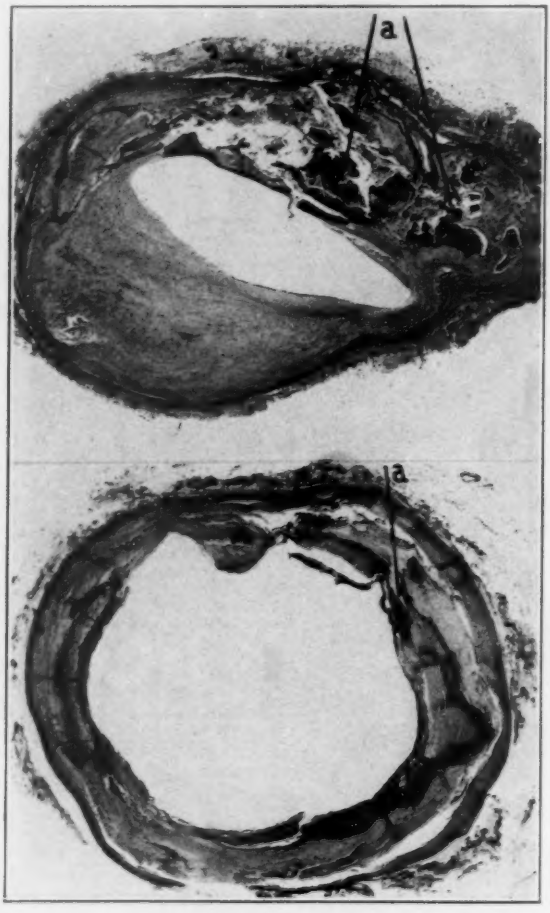


Fig. 6.—Upper and lower: Small hemorrhages, *a*, that were commonly seen in relation to calcareous plaques and were not associated with acutely occluding lesions.

far enough removed from hemorrhage to be considered independent of it. Chains of endothelial cells extended among the lipoid-containing cells, and lymphocytes, fibroblasts and other wandering cells were present.

The second group of lesions (figs. 4 and 5), in which hemorrhage was associated with more conspicuous proliferative changes, appeared to represent a lower grade of activity than the first group. The large lipoid-containing cells were absent. Lymphocytes, young capillaries, fibroblasts and endothelial cells were

intermingled with extravasated blood in the intimal stroma, although considerable variation was present in the proportion of cell types among the different lesions. Arterial thrombosis also was frequently related to lesions of this type.

The third group of lesions (fig. 6) was characterized by small localized hemorrhages, usually adjacent to calcified plaques. These lesions were not associated with acute arterial occlusion or thrombi and were seldom recognized grossly. Lipoid-containing cells were absent, and the degree of organization was variable. The relationship between these lesions and the calcium deposits was not clear. The process was apparently one of low grade activity and resulted in dense, calcified lesions. In general, this type of lesion was present among the older patients.

## COMMENT

The grouping of these lesions is general because it was not possible to divide them into clearcut types. An attempt has not been made to interpret the significance of the wide variation in the pathologic pictures among the lesions, except to consider it as representing grades of activity. This may be true to only a limited extent. Wherever intimal hemorrhage occurred, however, there appeared to be ample basis for it in the accompanying pathologic picture, and the elements which composed that picture were interpreted as being responsible not only for the hemorrhage but also for the associated occluding phenomenon and any coexistent thrombi.

## SUMMARY AND CONCLUSIONS

Hemorrhagic lesions were observed in the walls of the coronary arteries in 54 of 135 hearts (40 per cent) and were directly or indirectly related to acute occlusion of the coronary artery in 20. The lesions were characterized by hemorrhage associated with the presence of large lipoid-containing cells, proliferative intimal changes and organization. Smaller, less active lesions usually were found adjacent to calcified plaques. The intimal changes that coexisted with the hemorrhage appeared to represent the primary factor in the pathologic condition; the hemorrhage was secondary. It does not seem logical, moreover, that hemorrhage in itself can have produced the effects observed.

Mayo Foundation.

Mayo Clinic.

# FIBROSIS OF THE ENDOCARDIUM AND THE MYOCARDIUM WITH MURAL THROMBOSIS

## NOTES ON ITS RELATION TO ISOLATED (FIEDLER'S) MYOCARDITIS AND TO BERIBERI HEART

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Cardiac failure in young persons lacking the usual features of organic heart disease or associated renal lesions has frequently been ascribed to isolated (Fiedler's) myocarditis. A study of the reported cases of isolated myocarditis indicates a heterogeneous disease group related to known and to unknown infectious or toxic agents. Some changes are frankly inflammatory, others degenerative; some are acute, others subacute or chronic. Within the past few years evidence has accumulated that dietary deficiency can cause clinically evident heart disease which hitherto may have fallen into this vaguely defined classification. With advancing knowledge it becomes desirable to dissociate this group into more sharply defined types.

Recently we encountered 3 cases in which the patients died in the hospital of congestive failure of obscure origin. In all cases the patients were carefully studied during life and examined post mortem. Clinically and pathologically these cases resemble each other closely, and without recourse to the clinical history the anatomic diagnosis might well have been isolated myocarditis. Review of the history, clinical course and histologic data, however, suggests the possibility that the changes might have been due to long-continued dietary deficiency or defect in the absorption or utilization of certain accessory food factors. Similar lesions, including marked cardiac hypertrophy and mural thrombosis, have been ascribed to beriberi heart by Dock.[1] They differ from those of acute beriberi heart, adequately described by Wenckebach[2] and by Weiss and Wilkins.[3]

### REPORT OF THREE CASES

CASE 1.—*History.*—B. M., a 40 year old Chinese man, was admitted to New York Hospital on March 22, 1941. In 1933 the patient had lost 60 pounds (27 Kg.) in weight over a three month period. A roentgenogram revealed an enlarged heart and was suggestive of pulmonary congestion. The blood pressure was 110 systolic and 80 diastolic measured in millimeters of mercury. After restricted use of meat and salt the patient's weight decreased further to 135 pounds (61 Kg.). In 1936 edema of the ankles and nonproductive cough had appeared. Administration of a proprietary preparation of strophanthus and squill caused edema to disappear and relieved the cough. He had remained fairly well during the subsequent three years. When edema reappeared, mersalyl-theophylline solution was given fre-

From the Department of Medicine and the Department of Pathology of the New York Hospital and Cornell University Medical College.

1. Dock, W.: Marked Cardiac Hypertrophy and Mural Thrombosis in the Ventricles in Beriberi Heart, Tr. A. Am. Physicians **55**:61, 1940.

2. Wenckebach, K. F.: (*a*) Das Beri-beri Herz, Berlin, Julius Springer, 1934; (*b*) The Riddle of the Beriberi Heart, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 3, p. 1198.

3. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in the Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104, 1937.

quently over a two year period, with good response. During the year prior to admission the patient had again become dyspneic and edematous. Edema of the face had appeared four to five days before admission, when the swelling of his legs was so marked that fluid began to ooze. Inquiry revealed that his diet over several years had consisted of polished rice, white bread and Chinese vegetables, with occasional fish and pork, and had rarely included fruit.

*Physical Examination.*—On admission the rectal temperature was 36.6 C. (97.9 F.), the pulse rate 60 per minute, respirations 20 per minute and the blood pressure 126 systolic and 80 diastolic measured in millimeters of mercury. There were slight cyanosis of the lips and nail beds, massive anasarca and marked exertional dyspnea but no orthopnea. The skin of the entire body was dry and scaling. Over the distal portion of the extremities there were irregular macular patches of brownish discoloration with marked thickening and lichenification. There was fissuring of the skin at the commissures of the mouth and over the bridge and at the lateral angles of the nose. About the external nares were small, reddened areas of ulceration. Marked edema of the eyelids was present; the conjunctivas were engorged and discharged thick purulent material. The sides of the tongue were smooth and reddened. Over the lower lobe of the right lung there was slight dulness, and a few crepitant rales were audible at the base of each lung. The apical impulse of the heart was diffuse and was located in the left midaxillary line. On percussion the heart was enlarged both to the right and to the left. The cardiac sounds were distant and the rhythm totally irregular, and a soft systolic murmur was heard at the apex. The peripheral pulses were synchronous and equal, the vessels pliant. There was moderate venous engorgement with the edge of the liver palpable 7 cm. below the costal margin, and there was evidence of ascites. The spleen was not palpable. There was partial phimosis, and thick, greenish, purulent material covered the glans penis. Edema of the legs was marked, with fluid oozing through superficial cutaneous ulcerations. There was also edema of the arms and forearms. On neurologic examination there were generalized hyperesthesia to pinprick and tenderness of the calves and soles of the feet, and the ankle jerks were absent. Vibration and position senses were preserved, and the plantar responses were flexor.

*Laboratory Data.*—Urinalysis revealed a positive reaction for albuminuria (3 plus) but no sugar, cells or casts. Examination of the blood revealed 15 Gm. of hemoglobin per hundred cubic centimeters, 5,800,000 red cells, 9,600 leukocytes, a normal smear and differential count, a negative serologic reaction for syphilis (Kline test), 5.9 mg. of serum proteins per hundred cubic centimeters, 21 mg. of urea nitrogen per hundred cubic centimeters, an icteric index of 17 and 140 mg. of serum cholesterol per hundred cubic centimeters. Gonococci were not found in cultures of the urethral discharge. Gastric secretion contained 70 degrees of free hydrochloric acid after stimulation with histamine. Intravenous administration of 1,000 mg. of ascorbic acid yielded only 31 mg. in the urine during the test period. The vital capacity was 1,100 cc.

An electrocardiogram showed marked right axis deviation. Auricular fibrillation was present, with occasional ventricular premature contractions. The form of the T waves and the RT segments suggested myocardial damage but may have been due in part to recent administration of digitalis. Circulation time measured by sodium dehydrocholate was twenty-one seconds, and venous pressure was 210 mm. of solution of sodium chloride on direct measurement. A teleoroentgenogram (fig. 1) showed a small amount of fluid at the base of the left lung but gave no suggestion of parenchymal disease. The heart was enlarged in all diameters.

*Course of Illness.*—Ten milligrams of thiamine hydrochloride was given intravenously for three days, in addition to the daily oral dose of 60 mg. The parenteral dose was then increased to 50 mg. for eighteen days after which interval it was discontinued. During this regimen there was no change in symptoms, physical signs or the electrocardiographic pattern. Nicotinic acid was then employed, and the cutaneous lesions improved slightly, but at this time the ventricular rate increased to 104 per minute and the patient appeared more acutely ill. After the intramuscular administration of 5 cc. of a 10 per cent solution of digitan the apical rate decreased to 30 per minute. A diet high in vitamins supplemented with parenteral administration of vitamin preparations was begun. In addition, ammonium chloride and mercupurin were administered, and prompt diuresis resulted. Over a ten day period the body weight decreased from 64 to 54 Kg., with loss of edema. When the heart rate again became rapid, digitalis was given by mouth and the ventricular rate was maintained at 70 per minute by suitable doses. Auricular fibrillation persisted. The cutaneous lesions improved gradually, and the ulcerations on the legs healed. During the last month of life brewers' yeast was given in daily doses varying from 18 to 24 Gm., in addition to an oral dose of 30 to 60 mg. of thiamine hydrochloride. On the fifty-third day of hospitalization the temperature rose sharply to 39 C.

(102.2 F.). A red, swollen, sharply circumscribed area, typical of erysipelas, appeared on the face. The patient died suddenly the same day, May 12.

*Necropsy.*—Gross Examination: The right and the left pleural cavity contained 150 cc. and 100 cc., respectively, of clear straw-colored fluid and the peritoneal cavity contained 600 cc. The heart weighed 650 Gm., the chambers of both the right and the left ventricle being greatly distended; their walls measured 5 mm. and 10 mm., respectively. The myocardium of both ventricles was soft and red brown. On cut section congestion of the myocardial vessels was conspicuous. The endocardium of the left ventricle was thickened and contained one large area measuring 3 by 1 cm. in which the increase in fibrous connective tissue measured 1 mm. in thickness. Similar but smaller gray-white elevated patches were present in other places. A dry, friable thrombus was loosely attached to the pectinate muscles of the anterior and apical parts of the left ventricle. The right ventricle, especially the conus arteriosus, was markedly distended. In this chamber there were a few patchy areas of fibrous thickening of the endocardium similar to those seen in the left ventricle. The right auricle was moderately dilated,

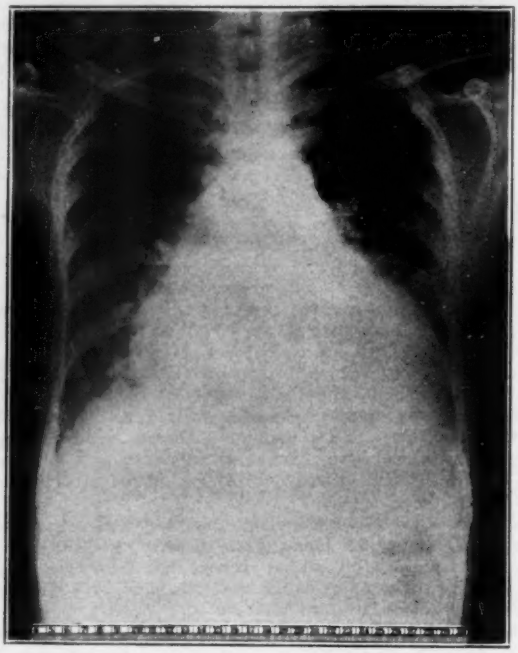

Fig. 1 (case 1).—A teleoroentgenogram taken three days after admission, showing a heart shadow enlarged both to the right and to the left, reaching the left lateral wall of the chest at the eighth rib posteriorly. This shadow obscures the lower portion of the left pulmonary field, but in addition there is increased density at the left costophrenic angle. A kymogram was abnormal only in flattening of the waves at the apex of the heart. This roentgenogram, as were all others reproduced here, was made at a 2 meter distance.

and a mural thrombus measuring 8 by 6 cm. in its greatest diameters adhered firmly to the auricular appendage. The left auricle and the valve leaflets were not altered.

Microscopic Examination: Sections of the myocardium showed a fine vacuolization of the muscle fibers in focal areas (fig. 2 *A* and *C*). There were only a few small areas in which the change similar to that designated by Wenckebach [2] as hydropic degeneration was noted. There was marked increase in fibrous connective tissue, and wide bands of connective tissue separated the muscle bundles in many places (fig. 2 *B*). In other areas there was merely slight interstitial edema. The smaller vessels, including capillaries of the myocardium, were engorged (fig. 2 *C*). The fibrous thickening of the endocardium observed in the gross specimen was striking in the sections (figs. 2 *B* and 3). Occasional islands of lymphoid cells with a

few monocytes and an occasional eosinophil were identified (fig. 2 *D*). The lungs were congested and edematous. In the lower lobe of the right lung a small infarct was undergoing organization. There was a thrombosed artery, and in the surrounding area were collections of large mononuclear cells containing golden yellow pigment. Similar cells were also encountered in smaller number in the alveolar spaces. The capillaries of the alveolar septums were engorged. Chronic passive congestion was also evident in the liver and the pancreas with slight increase in fibrous tissue in these organs. The spleen, kidneys and gastrointestinal tract also revealed passive congestion. A section of skin taken from the area of erysipelas

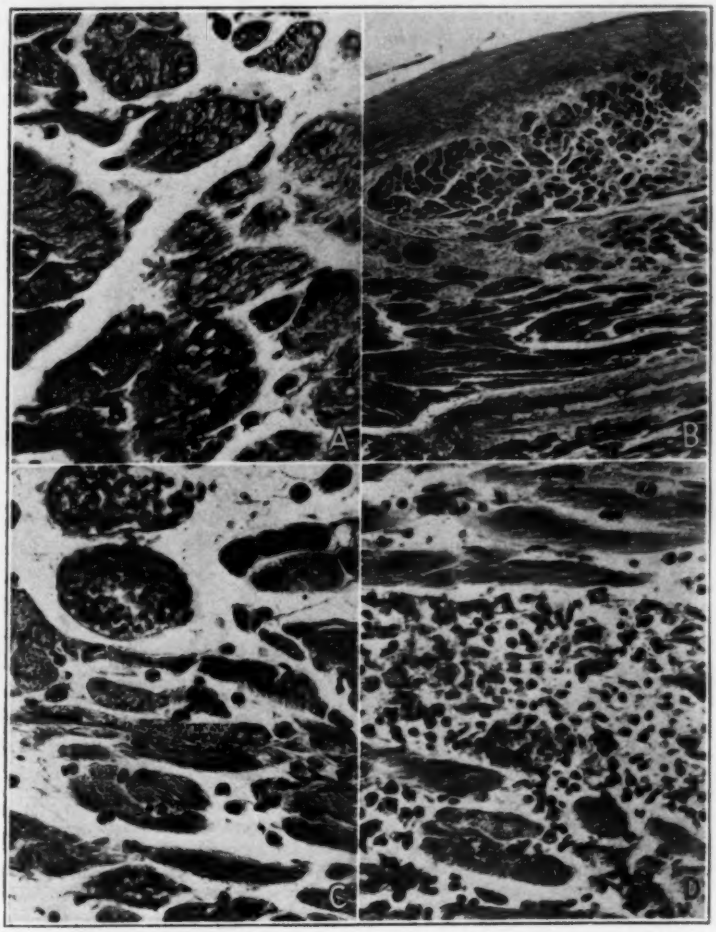


Fig. 2 (case 1).—Several sections of the myocardium. Part *A* illustrates the "moth-eaten" appearance of the muscle fibers and the engorgement of the smallest vessels (*venose Stauung* of Wenckebach). Part *D* illustrates a small focus of cellular infiltration.

showed diffuse suppurative inflammation of the corium with large numbers of polymorphonuclear leukocytes in microscopic abscesses. Sections from deeply pigmented areas of the skin showed thickening of the epidermis with hyperkeratinization. The papillae were irregular. There was an increase in the number of melanin-containing cells, and the pigment was also seen in large amounts in the squamous plates, a change regarded by Moore and Spies [4] as characteristic of pellagra.

4. Moore, R. A., and Spies, T. D.: Personal communication to the authors.

*Comment.*—This 40 year old Chinese man had symptoms and signs of congestive heart failure with remissions extending over an eight year period. His diet had been deficient at least during the period marked by heart failure. The changes in the skin were those of pellagra, and the lesions about the mouth indicated ariboflavinosis. Appropriate therapy failed to influence the course of illness, and death occurred after the development of erysipelas.

In addition to chronic passive congestion, autopsy showed an enlarged, greatly dilated heart. The conspicuous microscopic change was endocardial fibrosis in addition to myocardial fibrosis, slight focal lymphoid infiltration and vascular engorgement of the myocardium. "Hydropic degeneration," although present, was inconspicuous. Thrombi were encountered in the right auricle and the left ventricle, and a pulmonary infarct was evident.

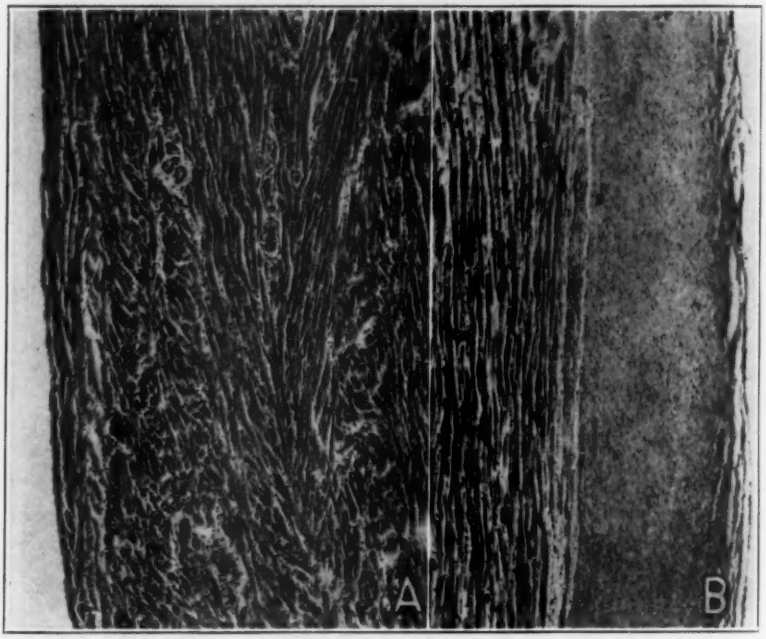


Fig. 3.—*A*, a section of normal heart muscle, showing the delicate appearance of normal endocardium, measuring only one to two cell layers in thickness. *B*, section of muscle from the heart of the patient in case 1. Contrast the extensive thickening of the endocardium.

Case 2.—*History.*—R. I., a 35 year old married Italian milliner, was admitted to New York Hospital on Sept. 1, 1940, because of dyspnea of five months' duration. At the age of 19 he had had "nephritis" characterized by albumin and casts in the urine which had cleared entirely two years before admission.

The present illness had extended over a nine month period, beginning with nonproductive cough and pain in the anterior portion of the chest on the right side. He had not had hemoptysis or symptoms of pulmonary tuberculosis. Four months after onset he had noted palpitation and a rapid pulse, and a teleoroentgenogram showed slight cardiac enlargement. The patient is said to have received digitalis, quinidine and salicylates for alleged rheumatic carditis.

Two months before admission, while the patient was convalescing, the nonproductive cough had returned. One week before admission dull pain had occurred in the midscapular region.

For four days persistent nausea permitted the taking of only liquid foods, and even these were vomited. The pulse became rapid at rest. There had been shortness of breath for five months on any effort but no orthopnea, paroxysmal dyspnea or edema of the ankles.

The patient had complained of vague gastric distress and avoided milk, fruit juice, tomatoes, spinach and other foods. During the present illness, his appetite had been particularly poor and he had lost 20 to 25 pounds (9 to 11 Kg.).

*Physical Examination.*—On admission the temperature was 38.4 C. (101.1 F.), the pulse rate 134 per minute, respirations 26 per minute and the blood pressure 100 systolic and 70 diastolic measured in millimeters of mercury. The patient was poorly nourished, pale and sallow with moderate cyanosis of lips and nail beds. There was dyspnea but no orthopnea. The skin and the scleras were icteric. The pulmonary fields were clear. The point of maximum impulse of the heart was felt 11 cm. from the midsternal line in the fifth left interspace. No shock or thrill was palpable. The heart rhythm indicated a normal sinus mechanism with occasional premature contractions. At the apex, the first sound was accentuated and a short, high-pitched, systolic murmur was heard. There was no diastolic murmur. After exercise there

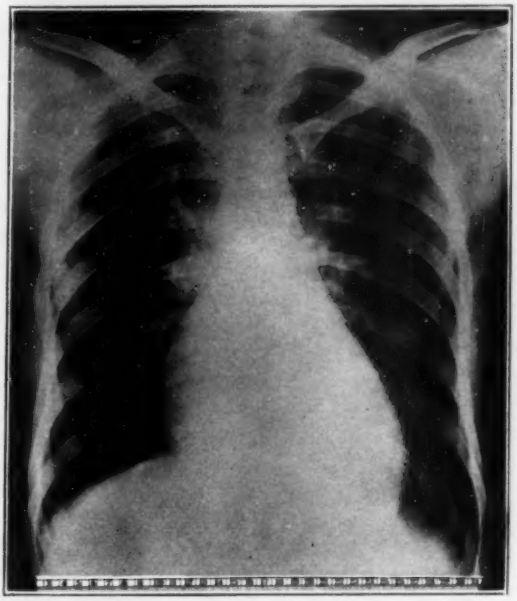

Fig. 4 (case 2).—A teleoroentgenogram taken shortly after admission, revealing enlargement of the heart shadow to the right and to the left with straightening of the left cardiac border. The major cardiac enlargement appears to occupy the position of the left ventricle. There is slight fulness in the region of the pulmonary conus. The transverse interlobar fissure on the right is accentuated. Irregular dense shadows are seen throughout both apexes with linear streaking connecting the apexes and the hilar regions.

was gallop rhythm at the apex. There were no palpable abdominal viscera, masses, ascites or peripheral edema.

*Laboratory Data.*—The specific gravity of the urine was 1.022; there was slight albuminuria, but the sediment was free of cells and casts. Examination of the blood yielded the following data: hemoglobin content, 13.5 Gm. per hundred cubic centimeters; red cell count, 5,200,000; leukocyte count, 11,100, with 89 per cent polymorphonuclears; smear, not remarkable; Kline reaction, negative; urea nitrogen, 29 mg. per hundred cubic centimeters; sugar, 91 mg. per hundred cubic centimeters; cholesterol, 158 mg. per hundred cubic centimeters; plasma chlorides, 460 mg. per hundred cubic centimeters, and icteric index 19. Four blood cultures were sterile. A van den Bergh test yielded an immediate direct positive reaction, and urobilinogen was present in the urine in a dilution of 1:80. In two hours there was an excretion of 80 per cent of a

test dose of phenolsulphonphthalein, while urea clearance in 2 tests was 61 and 55 per cent of normal. A roentgenogram (fig. 4) outlined a heart enlarged in all diameters with slight fulness of the pulmonary conus. It suggested old bilateral pulmonary tuberculosis with thickened pleura at the right apex. An electrocardiogram showed a right axis deviation. Normal sinus rhythm was present with sinus tachycardia and occasional premature contractions. The T waves were of generally low amplitude in all leads, and the T wave in lead I was abnormal in form. The P wave in lead II was of increased amplitude.

*Course of Illness.*—The patient had a low grade fever until shortly before death, the temperature at times being as high as 39.5 C. (103.1 F.). Food and fluids were limited because of nausea and vomiting. On the fifth day of hospitalization, he complained of pain in the chest on the left side posteriorly and respirations increased to 28 per minute. Over the lower lobe of the left lung, there was slight dulness and a few crepitant rales were audible. The radial pulse was feeble, at times imperceptible; the blood pressure was 90 systolic and 70 diastolic measured in millimeters of mercury. At this time the extremities were cold and cyanotic as in peripheral collapse. Cheyne-Stokes respirations were obvious. The obscure picture suggested Addison's disease, and adrenal cortical extract and dextrose in

Fig. 5 (case 2).—This photograph shows the gross appearance of the heart. There is slight dilatation of the right ventricle and marked dilatation of the left ventricular chamber. Thrombi are seen in the right auricular appendage but in greatest number in the left ventricle. There is a variable degree of organization of these thrombi. The thickening of the endocardium lining the left ventricle is apparent. Several large plaques of endocardial fibrosis are seen, the largest close to the aortic valves.

solution of sodium chloride were administered parenterally in addition to sodium chloride tablets given by mouth, but under this regimen pitting edema of the ankles soon developed. The venous pressure was estimated at 60 mm. of blood.

On the seventh day of hospitalization respirations became more embarrassed, and the patient received oxygen therapy. From time to time the shocklike picture reappeared. The blood urea nitrogen rose to 55 mg. per hundred cubic centimeters, while the carbon dioxide–combining power was 25 volumes per cent and the icteric index 38. Daily doses of adrenal cortical extract were continued, and thiamine hydrochloride was given daily by vein in 100 mg. doses. On the eighth day of hospitalization the skin had a mottled, cyanotic appearance. A tender edge of the liver was palpable 1 fingerbreadth below the costal margin. On the ninth day of his stay in the hospital the patient became stuporous. While the pulmonary fields remained relatively clear, the edge of the liver continued to be palpable. Edema of the ankles was persistent; there was swelling of the eyelids, and the skin was edematous everywhere, pressure

of the bedclothing leaving pit marks. The patient died quietly on September 11, the tenth day of hospitalization. There had been no response to thiamine or dietary measures.

*Necropsy.*—Gross Examination: The peritoneal cavity contained 500 cc. of clear yellowish liquid, but the other cavities did not contain excessive amounts of fluid. The heart weighed 500 Gm. The right auricle was slightly dilated, and its muscular wall was slightly thickened. The wall of the right ventricle measured 5 mm. in thickness, and its lumen was moderately enlarged. The myocardium of the left ventricle was not thickened, but the chamber was greatly dilated. Thrombi were encountered in the right auricular appendage and in the columnae carneae of the right ventricle, but in greatest number in the apical half of the left ventricle. The septal endocardium contained large patchy areas of fibrous thickening (fig. 5). The valve leaflets were normal. The coronary arteries and the aorta were delicate and free of intimal or medial change. The coronary veins were dilated. There was no evidence of active tuberculosis. No intrinsic lesion of the gastrointestinal tract was encountered.

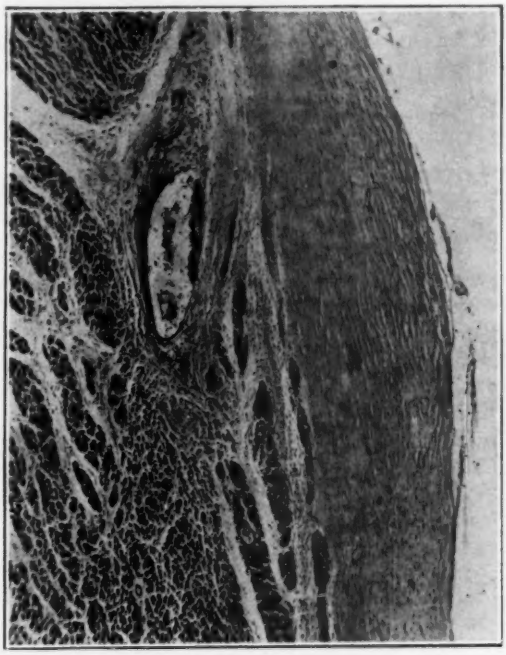

Fig. 6 (case 2).—A microscopic section of the myocardium, illustrating the fibrosis of the myocardium and the endocardium. It likewise demonstrates the degenerative change involving the subendocardial fibers with resultant fibrous tissue replacement.

Microscopic Examination: Section of the heart muscle, distant from the discrete endocardial plaques noted, showed a conspicuous fibrous thickening of the endocardium. Strands arising from the fibrous plate (fig. 6) extended deeply into the myocardium. Muscle fibers directly beneath and adjacent to the fibrous plaques showed advanced vacuolization. The incorporation of degenerating subendocardial fasciculi into the fibrous tissue meshwork could be discerned. These fibers stained in unusual fashion with the Masson stain specific for trichromes and with Mallory's stain specific for connective tissue. Organizing thrombi were seen to originate at or close to these areas of fibrosis. In the septum there were several areas of marked interstitial infiltration with polynuclear cells close to the areas of thrombosis at the apex. Sudan III stain revealed numerous small fat droplets in a few myocardial fibers. The capillaries and veins of the myocardium were engorged. There was no change in the vessel walls or in their lumens. In sections of the lung three organizing thrombi and a small recent infarct were seen. The alveolar septums were thickened and ischemic in some places, congested in other places. The liver showed advanced fatty degeneration with necrosis involving the central two

thirds of the lobule. Much blood pigment had been accumulated in mononuclear phagocytes. There was no renal or adrenal lesion.

*Comment.*—This 35 year old man was ill for nine months with obscure complaints largely referable to the gastrointestinal tract. He apparently had been a food faddist for many years, and during the period of final illness his diet was deficient in vitamins. His symptoms were not attributable at once to congestive heart failure, but the palpitation, tachycardia and dyspnea strongly suggested it. The physical findings likewise did not immediately indicate congestive heart failure, although the heart was enlarged. Right axis deviation in the electrocardiogram without demonstrable valvular heart disease was unusual; the alterations in T waves and RT segments were indicative of myocardial change. During his stay in the hospital there were several attacks of peripheral vascular collapse, and the patient suffered at least one episode of pulmonary embolism with infarction.

At autopsy the heart was extremely flabby and when suspended by the aorta gave the impression of a paper sac partially filled with fluid. There were thrombi within the chambers of the heart. On microscopic examination the myocardial changes were thought to represent idiopathic isolated myocarditis. Chronic passive congestion involved the lungs, the liver and the heart muscle itself, with central necrosis of the liver. There was excess fluid in the peritoneal cavity. The resemblance of the anatomic changes to those in case 1 and the clinical history, particularly the poor diet, raise the question whether this case also may be an instance of chronic deficiency of the vitamin B complex.

CASE 3.—*History.*—R. J., a 35 year old housewife was admitted to New York Hospital on June 24, 1939. One sister had died suddenly at the age of 22. (An incomplete coroner's report stated that there was cardiac hypertrophy with a yellowish myocardium, and "myocarditis" was assigned as the cause of death.)

Three months before admission the patient had had an attack of "bronchitis" with productive cough and pleural pain in the chest on the right side posteriorly. There was no hemoptysis. Occasionally she felt feverish and had night sweats. She became dyspneic and two weeks before admission began to sleep upright. One week before admission she had noted the onset of edema of the ankles followed by swelling of the legs. Two days prior to admission edema had involved the abdominal wall, the lower portion of the chest, the face and the eyes. Although the patient denied that she had any food idiosyncrasy, her husband's account indicated that her intake of vegetables, fruits and meats had probably been borderline. Since the onset of symptoms referable to the respiratory tract she had taken few green vegetables or cereals and little whole grain bread.

*Physical Examination.*—On admission the temperature was 37.6 C. (99.7 F.), the pulse 76 per minute, the respirations 20 per minute and the blood pressure 106 systolic and 88 diastolic measured in millimeters of mercury. The patient was thin and both dyspneic and orthopneic. There was moderate venous distention but no cyanosis. At the extreme base of the right lung there was an area of dulness through which breath sounds were not transmitted. There were a few basal rales bilaterally. The left border of dulness of the heart was 12 cm. from the midsternal line in the fifth interspace. The apical impulse was diffuse. There was no thrill palpable. Cardiac sounds were of fair quality; the rhythm indicated a normal sinus mechanism, and no murmurs were heard. The carotid and the brachial pulses were bounding. A tense, tender liver was felt 3 fingerbreadths below the costal margin, and the tip of the spleen was just palpable. There were no signs of ascites. No neurologic changes were discovered. There was a moderate pitting edema extending from the ankles over the tibias and up to the knees with slight pitting edema over the sacrum.

*Laboratory Data.*—The specific gravity of the urine varied between 1.006 and 1.032, and specimens showed albumin in moderate amount, but no casts were seen. The urea clearance was 65 per cent of normal. The hemoglobin content of the blood was 11 Gm. per hundred cubic centimeters, the red cell count was 4,300,000 per cubic millimeter and the leukocyte count was 7,300 per cubic millimeter. The blood smear and the differential count were not unusual. The corrected sedimentation rate was 0.1 mm. (normal 0.4 mm.) and the red cell volume 39 per cent. Repeated blood cultures were sterile. The serum per hundred cubic centimeters contained 163 mg. of cholesterol, 4.9 Gm. of proteins and 3.4 Gm. of albumin. The Kline reaction was negative. Fluid aspirated from the chest had a specific gravity of 1.009. On intravenous administration of 1,000 mg. of ascorbic acid 468 mg. was recovered in

the urine. Circulation time measured by sodium hydrocholate was thirty-eight and eight-tenths and thirty-six and two-tenths seconds, while the venous pressure was 172 mm. of solution of sodium chloride by direct measurement. An electrocardiogram showed a left axis deviation. The rhythm indicated a normal sinus mechanism. The conduction time of the QRS complex

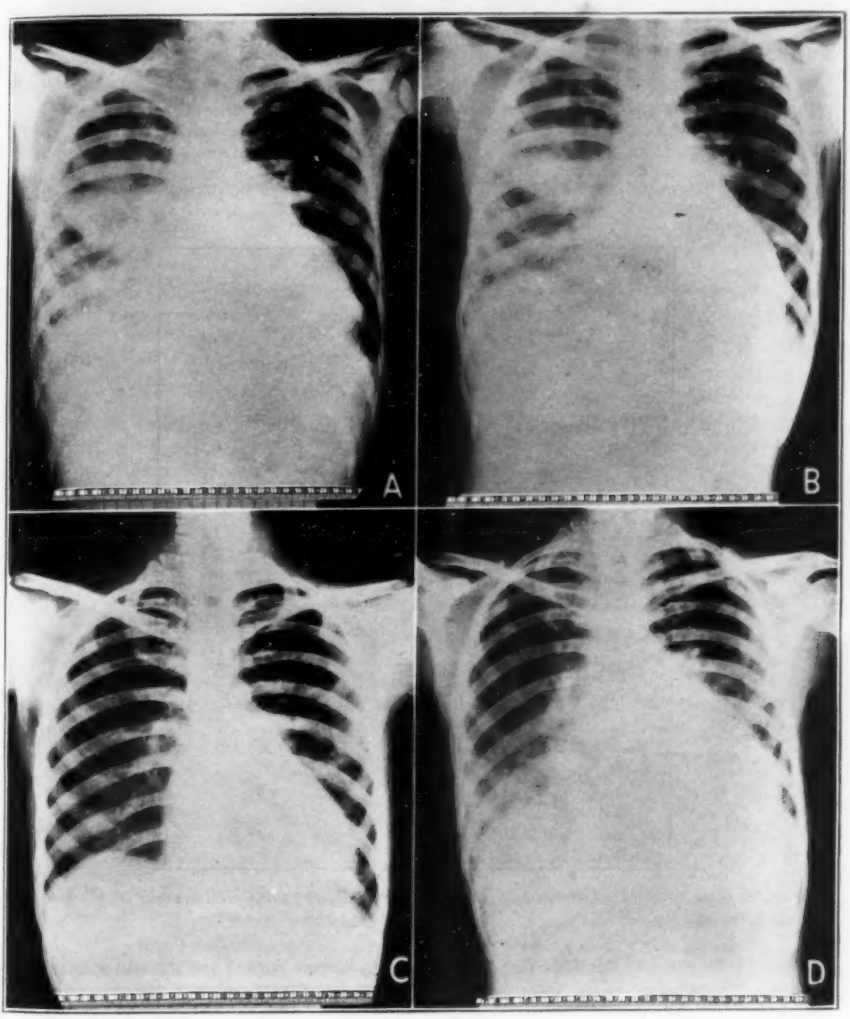


Fig. 7 (case 3).—*A*, teleoroentgenogram taken shortly after admission, showing an increase in the transverse diameter of the heart shadow, the enlargement being mostly in the left ventricular area. The pulmonary conus is definitely enlarged. Considerable fluid is accumulated in the right pleural space and extends into the minor fissure of the right side. *B*, a teleoroentgenogram taken after 1.8 Gm. of digitalis was administered within twenty-four hours, showing a decrease in the size of the heart and the pulmonary conus. *C*, a teleoroentgenogram taken at a time when the patient was markedly improved according to clinical standards, showing complete disappearance of the pleural effusion noted in parts *A* and *B*. The cardiac shadow, although smaller, continues to be enlarged especially the left ventricular portion. *D*, a teleoroentgenogram taken shortly before death, showing the heart shadow to have increased slightly in area. There is again increased density at the base of the right lung.

in lead II measured twelve hundredths of a second, and the T waves and the RT segments had the form seen in the left intraventricular heart block of the concordant type. The P waves were notched in all leads. Teleoroentgenograms made in this case are reproduced in figure 7.

*Course of Illness.*—Throughout her stay in the hospital the patient had a low grade fever. A diet high in vitamins and in carbohydrate was attempted, but because of refusal to eat tube feedings of high vitamin content had to be employed over a long period. The diagnosis of beriberi heart was proposed, and thiamine hydrochloride was given intravenously in 10 mg. doses daily for the first five days and then 20 mg. a day for the succeeding thirty-eight days with 8 Gm. of brewers' yeast daily. Nevertheless, dyspnea increased, and the patient became cyanotic, so that an oxygen chamber was employed. While this afforded slight relief, more marked improvement was noted with mercupurin therapy. Finally digitalis was given. The day following the circulation time was twenty-seven and six-tenths and twenty-eight and six-tenths seconds, and the venous pressure was 117 mm. of solution of sodium chloride. Two days after digitalization a complete left hemiplegia suddenly developed. The pressure and composition of the spinal fluid were normal. Under the usual supportive measures, there was a return of

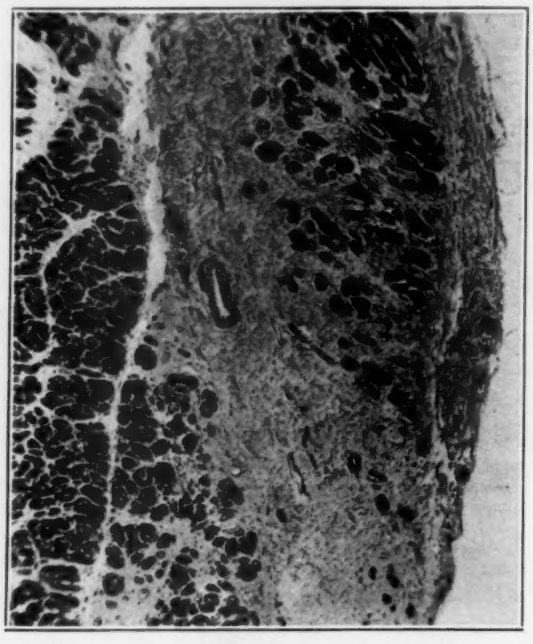

Fig. 8 (case 3).—A microscopic section of the myocardium, illustrating fibrosis of the endocardium and myocardium.

strength in the legs and arms, the deep tendon reflexes became normal and the sensory modalities returned, but weakness of the left side of the face and the plantar extensor response on the left side persisted. The phenomena of congestive heart failure cleared, and digitalis and diuretics were discontinued. Edema did not recur. The patient then tolerated restricted activity about the ward and finally was allowed home on the eighty-fourth day of her stay in the hospital. Within a few days she was readmitted with oliguria and dyspnea. There was edema of the face and dependent parts. The venous pressure was estimated at 150 mm. of solution of sodium chloride. A soft systolic murmur was heard at the apex. There was ascites. The liver was palpable 3 fingerbreadths below the costal margin. The blood picture was unchanged. The electrocardiographic pattern was little altered throughout the whole course of illness. Left intraventricular heart block continued to be present, and there was little change in the form of the T waves or the RT segments. Premature contractions of auricular, auriculoventricular nodal and ventricular origin were frequently recorded.

On the twelfth day after readmission the patient had a generalized convulsion lasting for three minutes, and on the thirty-fourth day this was repeated. There were no residual signs.

At no time was hypertension present. Ascites, hepatomegaly, pleural effusion, pulmonary congestion and periorbital and sacral edema continued. The patient showed a marked depressive trend, would not eat and vomited tube feedings. During the last eighteen days of life she received a daily dose of 90 mg. of thiamine hydrochloride and 20 Gm. of brewers' yeast by mouth. On November 27, the fifty-seventh day after readmission, she died suddenly.

*Necropsy.*—The peritoneal cavity contained 1,200 cc. of clear liquid, the pericardial cavity 250 cc. and the left pleural space 600 cc., while the right pleural space was obliterated by fibrous adhesions. The heart weighed 460 Gm.; the wall of the right ventricle measured 4 to 7 mm. and that of the left ventricle 12 mm. in thickness. The right ventricle was slightly dilated, and its myocardium was moderately fibrosed near the septum; the endocardium in this area was also thickened by fibrous tissue. The left ventricle was dilated, and the anterior, the lower and the septal third showed advanced fibrosis of the myocardium and the endocardium. The fibrosed endocardium measured from 1 to 2 mm. in greatest thickness. It encircled papillary muscles and columnae carneae and extended deeply into the myocardium. A large area of the anterior and the apical portion of the endocardium was covered with adherent recent thrombi. Microscopic sections did not show any inflammatory cells. The muscle fibers were thin and appeared atrophic in many places, but striations were well preserved. Some muscle fibers showed a moth-eaten appearance, not like the typical appearance of fatty degeneration which was seen in other areas. Chronic passive congestion was marked in the lungs, spleen, liver and pancreas. The kidneys in addition to chronic passive congestion showed several healed infarcts.

*Comment.*—This 35 year old woman was ill for eight months. The onset of her difficulty dated to an infection of the respiratory tract followed by dyspnea, orthopnea, gastrointestinal upset and peripheral edema. Congestive heart failure followed. There was enlargement of the heart, although there was no hypertension or evidence of valvular defect. Beriberi heart was considered, but there was little response to administration of thiamine hydrochloride or improved dietary regimen. The patient did not improve with continued administration of digitalis. Mercurial diuretics appeared to aid. Cerebral embolism occurred during her stay in the hospital.

Postmortem examination revealed evidence of congestive heart failure with ascites, hydrothorax and a small hydropericardium (250 cc.) and passive congestion of liver, lungs, spleen, kidneys and pancreas. There were organizing mural thrombi within the left ventricular chamber. These led to a cerebral embolus and the renal infarcts. The striking anatomic change was a marked endocardial fibrosis similar to that observed in cases 1 and 2.

## COMMENT

*Summary of Clinical and Anatomic Findings.*—In none of these 3 cases of congestive heart failure was valvular disease, hypertension or arteriosclerosis demonstrable. The patients, 2 men and 1 woman, were 35 to 40 years of age. In 1 case symptoms were present during eight years, with the final phase of illness occupying twelve months. In the other 2 cases the patients were ill for eight and nine month periods, respectively. In each there was progressive decline modified slightly by therapeutic measures. One patient, a Chinese man (case 1), had lived on a deficient diet over a long period; the other 2 patients had "poor appetites" and had taken diets probably borderline in their content of the vitamin B complex. In all cases the diet was deficient after the onset of the final illness.

The symptoms and signs on admission and during hospitalization pointed to disease of the cardiovascular system. Cyanosis was noted in 2 patients on admission and appeared in the third patient during hospitalization. Various other phenomena of congestive heart failure were observed with prolongation of circulation time and increase of venous pressure in 2 patients.

All patients showed albuminuria, probably related to chronic passive congestion, and the serum protein levels of 2 patients were 5.9 Gm. per hundred cubic centi-

meters (case 1) and 4.9 Gm. per hundred cubic centimeters (case 3). In these same 2 patients, the first with clinical pellagra and ariboflavinosis, the administration of 1,000 mg. of ascorbic acid intravenously resulted in the excretion of 31 mg. and 468 mg., respectively.

Electrocardiograms were altered, but no characteristic changes were observed. In case 1 auricular fibrillation was present; in the others normal sinus rhythm prevailed. In 2 cases there was right axis deviation. Left intraventricular heart block of the concordant type was present in the third case. Those patients with normal sinus mechanism showed various irregularities of rhythm. Premature contractions of ventricular origin occurred in case 2; in case 3 there were premature contractions, arising singly and in combination from the auricle, the auriculoventricular node and the ventricular muscle. Tall, notched P waves were seen in case 3. Alteration in the form of the T waves and the RT segments in each case pointed to myocardial change.

Several teleoroentgenograms, including anteroposterior and lateral views, were made at a 2 meter distance in each case. In case 1 (fig. 1) the shadow of the heart was tremendously enlarged in all diameters, particularly that of the left ventricle, and the pulmonary conus appeared full. A small amount of liquid obscured the left costophrenic angle. The heart shadow in case 2 (fig. 4) was increased to the right and the left with a straightening of the left cardiac border, the left ventricle constituting the major enlargement. On the first roentgen examination in case 3 (fig. 7 *A*) the transverse diameter of the heart was increased, the enlargement being mainly left ventricular, and the pulmonary conus was so prominent that mitral stenosis was suggested. Considerable fluid was apparent in the right pleural space with extension into the minor fissure. Further roentgen studies after digitalization (fig. 7 *B* and *C*) showed a slight and transient change in the cardiac outline. All patients had received digitalis without significant salutary effect. In 1 case the velocity of blood flow was enhanced by administration of the drug, the circulation time decreasing from thirty-seven and five-tenths seconds to twenty-eight and one-tenth seconds (average), while the venous pressure was lowered from 172 mm. to 117 mm. of solution of sodium chloride. These physiologic adjustments were not accompanied by clinical improvement, and the patient suffered cerebral embolism shortly after full digitalization. In the 2 cases (1 and 3) in which mercupurin was administered satisfactory diuresis, disappearance of edema with parallel loss in body weight and clinical improvement were noted. None made significant response to thiamine hydrochloride, nor was diuresis observed when the drug was given intravenously in doses ranging from 20 to 100 mg. over various periods. The course of illness was marked by progressive congestive heart failure with embolic phenomena.

The principal findings at necropsy in these cases agreed in several respects. In each there was evidence of cardiac failure with chronic passive congestion of the viscera. Pulmonary infarction was encountered in 2 cases, while in the third there were small renal infarcts. The heart was enlarged in each case, weighing 650, 500 and 460 Gm., respectively. The degree of hypertrophy and dilatation with respect to individual chambers has been described. Mural thrombi with varying degree of organization were seen in both right and left ventricles in 2 cases, while the left ventricle alone was involved in the third. There was no anatomic evidence of valvular defect, hypertension, arteriosclerosis or syphilis. Myocardial fibrosis was the conspicuous microscopic change. The most marked feature in all cases was the widespread endocardial fibrosis in both right and left ventricles, varying in its extremes from plaquelike deposits in case 2 and case 3 to the formation of a dense fibrous tissue plate covering the myocardium and investing the papillary muscles and trabeculae carneae in case 1.

*Isolated (Fiedler's) Myocarditis.*—Survey of the papers dealing with isolated myocarditis has failed to establish a uniform clinical or pathologic syndrome. Steffen [5] in 1888 reported the first cases of a condition designated acute myocarditis. In 1890 Fiedler [6] delineated the syndrome now bearing his name, while the adjective isolated was included by Sellentin [7] to indicate absence of inflammatory changes elsewhere. Aschoff [8] stated that he considered the lesions to be rheumatic in origin. In a search of the literature Scott and Saphir [9] found 36 reports with postmortem findings and tabulated the pertinent data in 30 cases. Bailey and Andersen [10] in their report reviewed this series, with criticisms. Thus, in the case reported by Rindfleisch [11] the condition probably was multiple pyogenic abscesses of the myocardium; in the second case of Steffen [5] and in the case reported by Baumgartner [12] the patient may well have had tuberculosis. Since the paper of Bailey and Andersen [10] many other reports have appeared.[13] In a recent review von Bonsdorff [14] indicated that in several of these [13] the classification of acute isolated myocarditis is not warranted. Several patients died suddenly after an acute illness; in others the course was chronic and marked by protean manifestations. In the former group careful histologic search disclosed small focal cellular infiltrations in the myocardium. In the cases in which illness was more chronic autopsy revealed varying pictures. A clear anatomic concept was not

5. Steffen, A.: Zur akuten Myokarditis, Jahrb. f. Kinderh. **27**:223, 1888.

6. Fiedler, A.: Ueber akute interstitielle Myokarditis. Festschrift zur Feier des 50-jahr. Bestehens des Stadtkrankenhauses zu Dresden-Friedrichstadt, Dresden, W. Baensch, 1890.

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9. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, Am. Heart J. **5**:129, 1929.

10. Bailey, F. R., and Andersen, D. H.: Acute Interstitial Myocarditis, Am. Heart J. **6**:338, 1931.

11. Rindfleisch, W.: Ein Fall von diffuser akuter Myokarditis, Inaug. Dissert., Munich, 1896; Thesis, Königsberg, M. Liedtke, 1898.

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13. (*a*) Boikan, W. S.: Myocarditis perniciosa, Virchows Arch. f. path. Anat. **282**:46, 1931. (*b*) de la Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis, Arch. Int. Med. **47**:942 (June) 1931. (*c*) Maslow, H. L., and Lederer, M.: Interstitial Myocarditis in a Child Nineteen Months of Age, Am. J. Dis. Child. **45**:807 (April) 1933. (*d*) Guizzetti, P.: Per la conoscenza della miocardite dell' atassia di Friedreich, Riv. di pat. nerv. **41**:545, 1933. (*e*) Carr, J. G., and Walsh, J. A.: Acute Infectious Myocarditis, Illinois M. J. **65**:134, 1934. (*f*) Maxwell, E. S., and Barrett, C. C.: Acute Interstitial Myocarditis: Report of a Case Following a Severe Dermatitis Due to Sulfur Ointment, Arch. Dermat. & Syph. **29**:382 (March) 1934. (*g*) Nelson, R. L.: Acute Diffuse Myocarditis Following Exfoliative Dermatitis, Am. Heart J. **9**:813, 1934. (*h*) Simon, M. A., and Wolpaw, S.: Acute, Subacute and Chronic Isolated Myocarditis: Report of a Case, Arch. Int. Med. **56**:1136 (Dec.) 1935. (*i*) Scott, R. W., and Simon, M. A.: Acute Isolated (Fiedler's) Myocarditis, Tr. A. Am. Physicians **51**:374, 1936. (*j*) Kjaergaard, H.: Acute Myocarditis, Acta med. Scandinav. (supp.) **78**:151, 1936. (*k*) Smith, F. M., and Stephens, R. L.: Acute, Subacute and Chronic Interstitial Myocarditis: Report of Six Cases, Tr. A. Am. Physicians **53**:120, 1938. (*l*) Freundlich, J.: Ueber isolierte, diffuse interstitielle Myocarditis, Ztschr. f. klin. Med. **133**:768, 1938. (*m*) Hansmann, G. H., and Schenken, J. R.: Acute Isolated Myocarditis, Am. Heart J. **15**:749, 1938. (*n*) Magner, D.: A Case of Fatal Subacute Myocarditis of Unknown Etiology, Am. J. M. Sc. **198**:246, 1939. (*o*) Helwig, F. C., and Wilhelmy, E. W.: Sudden and Unexpected Death from Acute Interstitial Myocarditis: A Report of Three Cases, Ann. Int. Med. **13**:107, 1939. (*p*) Brown, C. E., and McNamara, D. H.: Acute Interstitial Myocarditis Following Administration of Arsphenamines, Arch. Dermat. & Syph. **42**:312 (Aug.) 1940.

14. von Bonsdorff, B.: Less Common Causes of Heart Disease: Heart Disease of Unusual or Unknown Origin, Acta med. Scandinav. **100**:320, 1939.

possible on careful review of Fiedler's original case reports.[6] Karsner [15] defined acute isolated myocarditis as a

> . . . disease principally of early middle life, with insidious onset, signs of cardiac insufficiency and death after the lapse of a few months. The heart is hypertrophic, but without lesions of endocardium or pericardium. Microscopically there is interstitial infiltration of lymphocytes, leukocytes and large mononuclears with variable degrees of muscle destruction.

Most authors, including Scott and Saphir, have employed similar criteria. Nevertheless, in the first of the cases reported by Scott and Saphir, there were thrombi in the mural endocardium of the right ventricle, and in their second case thrombi were encountered in the left ventricle "where a few circumscribed areas of endocardial fibrosis were seen." The case report of de la Chapelle and Graef [13b] stated that "the endocardium was intact throughout, except at the apex of the left ventricle, where a firm, grayish-red thrombus was found attached to the endocardium." The microscopic examination of a section from the apex of the left ventricle "revealed a fairly advanced organizing process." For the most part these authors have included little detail of the patient's dietary habits.

*Etiologic Factors.*—The attempt to assign a common etiologic basis to "Fiedler's myocarditis" has likewise been unsuccessful. The role of infection of the respiratory tract has been emphasized in the earliest reports, but recent studies suggest many others factors. The myocardial disease in the case reported by Maxwell and Barrett [13f] followed a severe dermatitis due to sulfur ointment and was associated with staphylococcic bacteremia. Brown and McNamara [13p] called attention to 8 cases of "acute interstitial myocarditis" following the administration of arsphenamine and reviewed the reports of Nelson,[13g] Sikl,[16] von Zalka,[17] Stoeckenius [18] and Taussig and Oppenheimer.[19] A similar case apparently resulting from arsenical therapy for syphilis during pregnancy was observed in this hospital, and another case resembling the one reported by Guizzetti,[13d] characterized by myocardial edema and lymphocytic infiltration, occurred in a young diabetic patient with Friedreich's ataxia.[20] In a recent review on myocarditis by Saphir,[21] including Fiedler's myocarditis, the possible association with nutritional deficiency is not suggested.

*Beriberi Heart and "Idiopathic" Cardiac Hypertrophy.*—Certain cases previously reported as isolated myocarditis might have been classified as beriberi heart had more detailed information been available. Dock [1] described such lesions as we have encountered, including the endocardial fibrosis, although it was not so widespread. Similar cases were reported by Levy and Rousselot [22] and by Levy and von Glahn,[23] although they were interpreted differently. In comment on Dock's paper Levy [24] denied the relation of illness in the cases which he reported

15. Karsner, H. T.: Human Pathology, ed. 4, Philadelphia, J. B. Lippincott Co., 1935, p. 460.
16. Sikl, H.: Eosinophile Myocarditis als idiosynkrasische-allergische Erkrankung, Frankfurt. Ztschr. f. Path. **49**:283, 1936.
17. von Zalka, E.: Ueber einen seltsamen Fall von Polymyositis, Virchows Arch. f. path. Anat. **281**:114, 1931.
18. Stoeckenius, W.: Beobachtungen an Todesfällen bei frischer Syphilis, Beitr. z. path. Anat. u. z. allg. Path. **68**:185, 1921.
19. Taussig, H. S., and Oppenheimer, E. H.: Severe Myocarditis of Unknown Etiology, Bull. Johns Hopkins Hosp. **59**:155, 1936.
20. Unpublished data.
21. Saphir, O.: Myocarditis: A General Review with an Analysis of Two Hundred and Forty Cases, Arch. Path. **32**:1000 (Dec.) 1941; **33**:80 (Jan.) 1942.
22. Levy, R. L., and Rousselot, L. M.: Cardiac Hypertrophy of Unknown Etiology in Young Adults, Am. Heart J. **9**:178, 1933.
23. Levy, R. L., and von Glahn, W. C.: Further Observations on Cardiac Hypertrophy in Adults, Tr. A. Am. Physicians **52**:259, 1937.
24. Levy, R. L., in discussion on Dock.[1]

to a deficiency of vitamin B complex. He reasoned that vitamin $B_1$ failed as a therapeutic agent, remissions occurred without the use of vitamin $B_1$ (in addition to the general hospital diet) and that the pathologic lesion was not like that of beriberi. In all of our cases there were remissions without therapy with the vitamin B complex. In the first case remissions were characteristic of an eight year period of illness. Moreover, none of our patients made significant response to thiamine hydrochloride in recommended dosage. The patient in the first case reported by Levy and Rousselot [22] had "slight thickening of the septal surface of the endocardium which at this place measured 2 mm." In their second case the condition might represent the intermediate stage between the acute form of beriberi heart and the more chronic disease being described in this report. The fibers of the heart muscle showed an advanced stage of hydropic degeneration. Vacuolization was so pronounced that "only a little remnant of sarcoplasm remained against the cell membrane making the muscle fibers appear as empty envelopes" (figures 5 and 6 of the paper by Levy and Rousselot [22]). There was advanced fibrosis; "everywhere throughout the heart, the knife, as it cut, encountered unusual resistance." Thickening of the endocardium was conspicuous as "it was no longer possible to see the underlying myocardium." In their third case there were "thin streaks of endocardial thickening over the interventricular septum." In all cases there were mural thrombi in the ventricles and pulmonary and systemic infarcts. The authors did not review their patients' dietary habits. Kugel and Stoloff [25] described 7 cases of "idiopathic hypertrophy of the heart" in infants, noting endocardial fibrosis in all of them. These authors suggested that among other causes "history of avitaminosis (beriberi)" ought to be excluded. Endocardial fibrosis was described in one of Sellentin's protocols [7] as early as 1904. The formation of mural thrombi is probably facilitated by the plaquelike thickenings of endocardium and may mark a terminal stage in the disease process. The problem is whether myocardial fibrosis represents a late stage in the development of beriberi heart.

*Experimental Production of Beriberi Heart.*—Attempts to produce cardiac lesions in experimental animals by diets deficient in the vitamin B complex have not been entirely successful. Lack of knowledge of spontaneous myocarditis and of changes due to vitamin deficiency in animals limit such observations. Miller [26] encountered myocardial lesions in 60 per cent of a rabbit colony which was presumably healthy. Thomas, Mylon and Winternitz [27] produced myocardial lesions by keeping rats and pigs on a diet deficient in potassium as well as in the vitamin B complex. It is possible that in the pathogenesis of chronic beriberi heart factors other than a deficiency of thiamine hydrochloride participate. Swank [28] found that in about half of the hearts of pigeons "chronically deficient in thiamin, early changes were evident, such as focal necrosis with inflammatory cell infiltration." Porto and de Soldati,[29] studying cardiac changes in rats and dogs, reported "anemic infarcts" together with interfascicular edema, perinuclear vacuolization

25. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and in Young Children, Am. J. Dis. Child. **45**:828 (April) 1933.

26. Miller, C. P.: Spontaneous Interstitial Myocarditis in Rabbits, J. Exper. Med. **40**:543, 1924.

27. Thomas, R. M.; Mylon, E., and Winternitz, M. C.: Myocardial Lesions Resulting from Dietary Deficiency, Yale J. Biol. & Med. **12**:345, 1940.

28. Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71**:683, 1940.

29. Porto, J., and de Soldati, L.: Infarcto de miocardio aparecido en un perro en avitaminosis $B_1$, Rev. Soc. argent. de biol. **15**:426, 1939.

and marked vacuolization of the conduction system. Leblond and Chaulin-Servinière [30] studied beriberi in monkeys and concluded that partial rather than complete thiamine deficiency was the cause of chronic heart disease.

*Clinical and Anatomic Features of Beriberi Heart.*—Cardiac failure in beriberi has been explained by Wenckebach [2] with the myogenic, as opposed to the neurogenic, theory. He postulated that the heart muscle lost its power of contraction and its resistance against stretching. In the cases which he reported the right ventricle, especially the conus arteriosus, was dilated, while the left ventricle did not appear to have been overloaded. There is a lowered peripheral resistance with rapid stasis of blood in the capillaries at the arteriolar end. The systolic energy is not decreased, and the right side of the heart is filled under high venous pressure; "the blood runs to the heart in an attempt to burst it apart" (Wenckebach). The clinical picture is, however, not always so clear. Keefer,[31] studying beriberi in China, indicated that dilatation was not limited to the right ventricle. Weiss and Wilkins [3] likewise noted pulmonary engorgement with dyspnea and orthopnea and other evidence of "left sided failure." These authors did not regard peripheral neuritis as a necessary accompaniment of such deficiency.

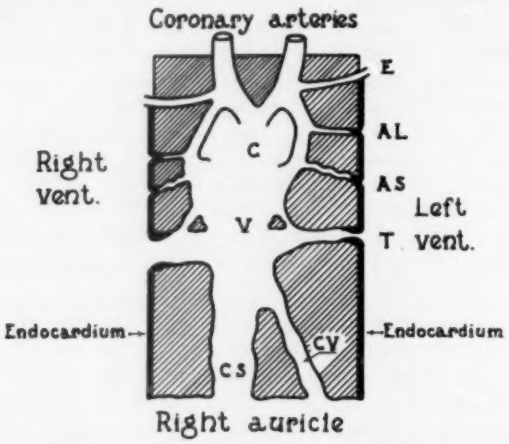


Fig. 9.—Wearn's schematic representation of the coronary circulation is here modified to include thickening and fibrosis of the endocardium. The effect of such change on the nutrition of the myocardium is apparent. The following abbreviations have been employed: *E*, extracardiac branches; *AL*, arterioluminal vessels; *AS*, arteriosinusoidal vessels; *T*, thebesian veins; *V*, coronary veins; *CV*, coronary veins, and *CS*, coronary sinus.

In the 3 cases reported here a clinical syndrome with fairly uniform features was present. The usual precipitating causes of heart failure were notably absent. Careful questioning elicited the history suggestive of dietary deficiency, but accurate studies of absorption and utilization of the vitamin B complex were not possible. Autopsy revealed the features of congestive heart failure. The hearts were enlarged and dilated. Mural thrombosis had occurred and had led to embolism. Myocardial fibrosis has usually been ascribed to diminution of the myocardial blood supply [32] leading to scattered areas of degeneration and replacement fibrosis.

30. Leblond, C. P., and Chaulin-Servinière, J.: Spontaneous Beriberi of the Monkey as Compared with Experimental Avitaminosis, Am. J. M. Sc. **203**:100, 1942.

31. Keefer, C. S.: The Beriberi Heart, Arch. Int. Med. **45**:1 (Jan.) 1930.

32. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937, pp. 427-428.

The observations here described suggest that it may also be the end result of nutritional deficiency. Investigation must still ascertain whether the subendocardial fibers are more susceptible to hydropic degeneration and whether fibrosis supervenes hydropic degeneration. It is possible that endocardial and myocardial fibrosis may render the disease process self aggravating and self perpetuating in the nature of a vicious cycle. Muscle degeneration leads to fibrosis and in turn to further degeneration of enclosed muscle fibers, aggravated by rhythmic stretching of the heart, produced or facilitated by some factor not yet recognized. It is conceivable that some myocardial functional change coexists with a nutritional deficiency; for example, the stimulus of diastolic stretching may fail to elicit the usual response leading to hypertrophy when the muscle fibers are injured by hydropic degeneration, but interstitial fibrosis once established may in itself be an aggravating factor. Wearn [33] reviewed the communication of vessels in the myocardium with the ventricular cavities, designating them as "arterio-luminal" and "arterio-sinusoidal." A diagram of Wearn's has been modified to show the impairment of blood supply as a consequence of endocardial fibrosis (fig. 9).

Whether the cases here described actually represent chronic beriberi heart, or are at all the consequence of nutritional deficiency, is not adequately proved. The clinical and anatomic findings parallel previously reported instances of isolated (Fiedler's) myocarditis. Study of the reported cases indicates that "isolated myocarditis" represents a heterogeneous collection of acute and chronic forms of myocardial disease, marked by inflammatory or degenerative changes with and without fibrosis. Further separation of the complex into well defined types is desirable. Evaluation of available data suggests that the 3 cases outlined here represent a chronic form of heart disease, possibly caused by or associated with dietary deficiency. The purpose of this report is to call attention to this type and to stimulate further inquiry into its pathogenesis.

## SUMMARY

Three cases of heart failure in young adults which is not attributable to arteriosclerosis, hypertension or valvular heart disease are reported.

The most striking pathologic features are endocardial and myocardial fibrosis and cardiac hypertrophy and dilatation in the absence of vascular or valvular change. The endocardial fibrosis and cardiac failure predispose to mural thrombosis with emboli. These changes resemble those previously described in the literature under the term isolated myocarditis.

The question is raised whether these changes could have been associated with deficient diet and could represent a variant of beriberi heart.

NOTE.—Since preparation of this manuscript 2 additional cases have been encountered.

CASE 4.—A 63 year old bachelor, chronically addicted to alcohol, with irregular eating habits, gave evidence of congestive heart failure extending over four years. At autopsy there were endocardial and myocardial fibrosis, mural thrombosis and pulmonary infarction.

CASE 5.—A 54 year old man with "poor" appetite and "chronic indigestion" of twenty years' duration gave a history of ten years of marked chronic alcoholism. Symptoms of heart failure extended over three years. At autopsy the heart was dilated and showed myocardial and endocardial fibrosis, while the coronary arterial bed was entirely normal on examination, which included injection. Mural thrombosis of the right ventricle had led to pulmonary infarcts.

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# STREPTOCOCCIC BACTEREMIA CURED WITH SULFADIAZINE

## REPORT OF A CASE OF INFECTION CAUSED BY HEMOLYTIC STREPTOCOCCI OF LANCEFIELD GROUP C, WITH A REVIEW OF THE LITERATURE AND PRESENTATION OF IMMUNOLOGIC DATA

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The classification of hemolytic streptococci proposed by Lancefield [1] in 1933 has proved an important advance in the study of streptococcic infections. Using the precipitin technic, based on the presence in hemolytic streptococci of a specific carbohydrate obtainable by acid hydrolysis, she divided these organisms into several groups, designated by the letters A to K, inclusive, and pointed out that most streptococcic infections in human beings were caused by members of her group A. Subsequent studies have confirmed this observation,[2] but a good many cases have been reported in which etiologic organisms were members of certain of the other groups.

Group B strains have been isolated in cases of suppurative arthritis,[3] puerperal sepsis [4] and endocarditis.[5] Severe cases of endocarditis [6] and puerperal sepsis [4a] have also been ascribed to members of group G. The status of group D organisms is beyond the scope of this paper and will be discussed elsewhere.[7] Although frequently recovered from patients, their role in the causation of disease is often difficult to ascertain. Group F strains have been isolated from infected wounds and sinuses [8] and from the throats of patients with glomerulonephritis.[9] As far

From the Department of Medicine, Stanford University School of Medicine.

1. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571, 1933.

2. (*a*) Rantz, L. A., and Keefer, C. S.: The Distribution of Hemolytic Streptococci, Groups A, B, and C in Human Infections, J. Infect. Dis. **68**:128, 1941. (*b*) Hare, R.: Sources of Hemolytic Streptococcal Infection of Wounds, Lancet **1**:109, 1940.

3. Rantz, L. A.: Suppurative Arthritis Due to a Hemolytic Streptococcus of the Lancefield Group B: A Case Report, Ann. Int. Med. **13**:1744, 1940.

4. (*a*) Lancefield, R. C., and Hare, R.: Serological Differentiation of Pathogenic and Non-Pathogenic Strains of Hemolytic Streptococci from Parturient Women, J. Exper. Med. **61**:335, 1935. (*b*) Fry, R. M.: Fatal Infections by Hemolytic Streptococcus Group B, Lancet **1**:199, 1938.

5. Rosenthal, A. H., and Stone, F. M.: Puerperal Infection with Vegetative Endocarditis, J. A. M. A. **114**:840 (March 9) 1940.

6. MacDonald, I.: Fatal and Severe Human Infections with Hemolytic Streptococci Group G (Lancefield), M. J. Australia **2**:471, 1939.

7. Rantz, L. A., and Kirby, W. M. M.: Enterococcic Infections: An Evaluation of the Importance of Fecal Streptococci and Related Organisms in the Causation of Human Disease, Arch. Int. Med. **71**:516 (April) 1943.

8. Longcope, W. T.: Studies of the Variations in the Antistreptolysin Titer of the Blood Serum from Patients with Hemorrhagic Nephritis: II. Observations on Patients Suffering from Streptococcal Infections, Rheumatic Fever and Acute and Chronic Hemorrhagic Nephritis, J. Clin. Investigation **15**:277, 1936.

9. Long, P. H., and Bliss, E. A.: Studies upon Minute Hemolytic Streptococci: IV. Further Observations upon the Distribution of Ordinary and Minute Beta Hemolytic Streptococci in Normal and Diseased Human Beings, J. Infect. Dis. **62**:52, 1938.

as can be determined, infections due to members of groups E, H and K have not been reported.

Group C organisms are probably responsible for more infections than organisms of any group other than A.[2b] It is not to be inferred, however, that group C strains are common in relation to members of group A, which cause over 95 per cent of all streptococcic infections. Less than 100 cases of infection caused by group C organisms are recorded, in contrast to the many thousands of infections caused by group A organisms that can be found in the literature. Scarlet fever,[2b] puerperal infection,[10] erysipelas [11] and infections of wounds [2b] are the chief conditions in which group C organisms have been isolated. A knowledge of the natural distribution of these organisms is important in evaluating their role in infections in human beings. In general, it can be said that in normal persons group C strains are isolated from the same sources as are members of group A but much less frequently. For example, hemolytic streptococci of group A are recovered from the normal human nasopharynx three or four times as often as are hemolytic streptococci of group C.[12]

The purpose of this paper is to present a case of bacteremia in which hemolytic streptococci of group C were the infectious agents and in which recovery followed administration of sulfadiazine. In addition, bacteriologic and immunologic data will be presented and will be discussed in relation to the Lancefield groups as a whole.

## REPORT OF CASE

*History.*—The patient was a 65 year old single white American janitor, who entered Stanford University Hospitals on Nov. 1, 1941, complaining of generalized pains and shortness of breath of several months' duration. The history was not considered entirely complete or reliable because of the patient's faulty memory for recent events.

The familial history and the past history were not contributory. The patient was well and strong until about five months before admission, when he had an episode of vomiting and diarrhea, which he attributed to eating poisoned meat. After this he refused to eat meat, but his diet was otherwise probably adequate. He felt certain that this episode marked the beginning of his present illness. Easy fatigability and dyspnea on the slightest exertion appeared almost immediately. Generalized "pains in the muscles" also appeared, which were deep and "felt as if they were in the bones," especially in the legs.

Two months before entry he suddenly noted a sharper, more constant pain in the left hip, which caused limitation of motion of that joint. This occurred at intervals until the time of entry. General fatigue, muscle aches and shortness of breath became gradually more pronounced, although he remained ambulatory. Thirteen days before admission he was seized with a sharp, severe pain in the chest on the left side, just below the nipple, which radiated to both axillas and caused difficulty in breathing. He sat up all night, and the next morning his pain gradually disappeared. After this episode, he became weaker and the muscular pains became more pronounced. One week before entry he had a moderately severe shaking chill, the first he had experienced. Chilly sensations recurred at intervals during the next several days, but he was not aware that he had any fever. At the time of admission there was a superficial ulcer on the left thigh, which he had not noticed. Moderate tenderness over the left parotid region had been present for several days. A loss of weight of 10 to 15 pounds (5 to 7.5 Kg.) was said to have occurred during the past four or five months.

*Physical Examination.*—On admission the patient was slender, poorly nourished and acutely ill. The temperature was 40 C. (104 F.); the respirations were 22 per minute; the pulse rate was 84 per minute, and the blood pressure was 150 systolic and 80 diastolic. Small, pinkish red, maculopapular lesions were irregularly scattered over the skin of the entire body.

10. Congdon, P. M.: Streptococcal Infection in Childbirth and Septic Abortion: Source of Infection and Grouping of Hemolytic Strains, Lancet **2**:1287, 1935. Rosenthal and Stone.[5]

11. Hare, R.: The Classification of Hemolytic Streptococci from the Nose and Throat of Normal Human Beings by Means of Precipitin and Biochemical Tests, J. Path. & Bact. **41**:499, 1935. Plummer, H.: Serological Study of Hemolytic Streptococci, J. Bact. **30**:5, 1935.

12. (*a*) Rantz, L. A.: The Hemolytic Streptococci: Studies on the Carrier State in the San Francisco Area, with Notes on the Methods of Isolation and Serological Classification of These Organisms, J. Infect. Dis. **69**:248, 1941. (*b*) Hare.[2b]

A good many of these were pustules. On the lateral aspect of the left thigh there was a superficial ulcer, about 1 cm. in diameter, which had apparently been present for several days. In addition to these lesions, there was a generalized reddening of the skin over parts of the trunk and extremities which was similar to the rash seen in scarlet fever. Small hemorrhagic areas were also present beneath the skin of the extremities. There were slight tenderness and swelling in the region of the left parotid gland. The throat was slightly injected, and the tongue was dry. The chest was emphysematous but otherwise clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. Examination of the abdomen yielded nothing remarkable. There were signs of moderately advanced peripheral arteriosclerosis. Generalized muscular tenderness was present, most markedly in the calves. The results of the physical examination were otherwise irrelevant.

*Laboratory Examination.*—Examination of the blood revealed a hemoglobin content of 9.2 Gm. per hundred cubic centimeters (Sahli), a red cell count of 2,200,000 and a white cell count of 680, with a differential count of 27 per cent polymorphonuclear leukocytes, 64 per cent lymphocytes, 6 per cent eosinophils and 3 per cent monocytes. The red cells showed marked anisocytosis, poikilocytosis and polychromasia. Toxic granules were present in the polymorphonuclear leukocytes. The platelets numbered 40,000. The percentage of reticulocytes was 1. The hematocrit reading was 23. The sedimentation rate was 70 mm. in thirty minutes. The

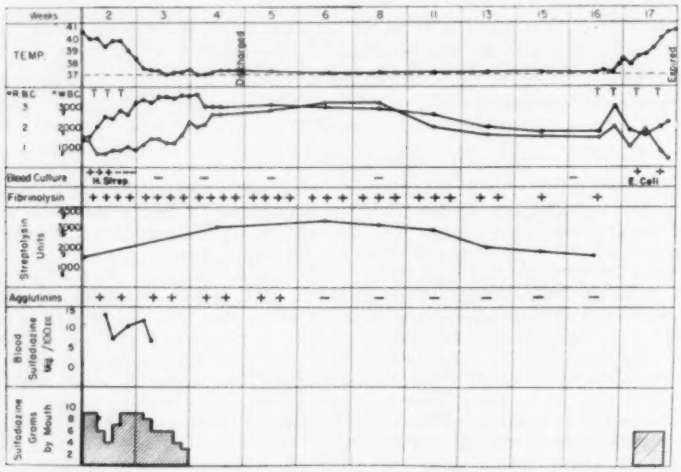


Fig. 1.—Clinical course of a patient with bacteremia caused by hemolytic streptococci of Lancefield group C.

direct van den Bergh reaction was negative, and the indirect reaction was positive (0.64 units). The icterus index was 5. There was urobilinogen in the urine, the reaction for it being positive in a dilution of 1:128. The blood contained 54 mg. of urea per hundred cubic centimeters. The stool and urine were normal; there was no Bence Jones protein in the urine. The Wassermann reaction was negative. A blood culture was positive for hemolytic streptococci, Lancefield group C, with six colonies per cubic centimeter.

*Diagnosis.*—It was not clear at first whether the aplastic anemia was due entirely to the infection of the blood stream or whether the bacteremia was merely an intercurrent process developing during the course of some underlying disease. Sepsis was the immediate problem, however, and therapy was directed toward the eradication of the streptococcic infection.

*Course of Illness.*—The important data are summarized in figure 1. Since the first chill occurred one week before entry, it is assumed that the bacteremia began at that time. Admission to the hospital, then, was during the second week of the illness.

Although the patient's prognosis seemed poor on admission, there was rapid improvement after therapy with sulfadiazine was begun. The blood culture was negative for hemolytic streptococci on the third day of hospitalization, the rash had disappeared and most of the pustules were beginning to heal within four days, and at the end of the eighth day the temperature was normal. Three blood transfusions were given during the first week. The remainder of the course of illness during the hospitalization was uneventful. Except for a

moderate rise in the red cell and the white cell count, the blood picture remained much as it was on admission. A biopsy of bone marrow was done two weeks after entry, and the marrow was found to be hypoplastic. Inactivity of myelocyte multiplication, with delayed maturing of these cells to the polymorphonuclear stage, appeared to be the chief cause for the hypoplasia of the white cell series. Except for moderate weakness the patient felt entirely well when he went home on the eighteenth day after admission.

His subsequent course was followed in the outpatient department for twelve weeks, and during this time he was afebrile, and his only complaints were easy fatigability and precordial pain and dyspnea on exertion. The blood picture remained essentially unchanged, except that the red cell and the white cell count fell gradually, in spite of intensive therapy with various preparations of iron and liver. A roentgen survey of the long bones during this period did not reveal any abnormalities.

The patient reentered the hospital during the fifteenth week after the first admission. Physical examination failed to reveal anything new, except for a fissure *in ano*, which was painful. The results of laboratory examination were as follows: red cell count, 1,052,000; hemoglobin concentration, 34 per cent; white cell count, 1,400, with a differential count of polymorphonuclear leukocytes 16 per cent (64), lymphocytes 74 per cent and monocytes 16 per cent; hematocrit reading, 14; platelet count, 18,000; reticulocyte percentage, 0.3; urine and stool, normal; Bence Jones protein in urine, none, and blood urea, 33 mg. per hundred cubic centimeters.

Two blood transfusions were given, after which the red cell count rose to 2,200,000. The patient was then transferred to another hospital. Within two days his temperature began to rise, and a blood culture was positive for Escherichia coli. The septic process continued in spite of therapy with sulfadiazine and transfusions, and the patient died sixteen weeks after the onset of the bacteremia caused by hemolytic streptococci.

*Autopsy.*—Results of a postmortem examination contributed little. The bone marrow presented the same hypoplastic picture which was seen in the biopsy specimen. No other significant lesions were encountered.

*Comment.*—The cause of the aplastic anemia is not known, but it is quite certain that the streptococcic infection was not responsible. The patient had had symptoms of the underlying disease for two or three months before chills and fever appeared, suggesting that the bacteremia was an intercurrent episode, made possible partly by a lowering of the natural cellular defense mechanisms. Further, an aplastic blood picture is rarely if ever produced by acute infections. The absence of an elevation of blood bilirubin suggests that no acute hemolytic process had occurred. Finally, the bone marrow did not resume its normal activity after the infecting organisms had been cleared from the blood stream, indicating that the depression of hemopoietic activity was caused by some other agent.

The response to sulfadiazine was remarkable, considering the age and the generally poor condition of the patient. It is thought that the action of sulfonamide compounds in vivo is bacteriostatic, rather than bactericidal, inhibiting the growth of organisms and allowing the phagocytes to engulf and destroy them. It is impressive, then, to observe such a prompt recovery in this elderly, debilitated man, with severe anemia and a white cell count of less than 1,000. The transfusions were undoubtedly of considerable aid in supplying the deficient blood elements. The other important factor, of course, is the patient's antibody response, and it will be shown later that this patient had a high titer of circulating antibodies.

The source of infection was probably the superficial ulcer on the left thigh, since there was no other obvious focus, and since group C organisms are occasionally isolated from human skin.[2b]

The rash, which was similar to that seen in scarlet fever, was of considerable interest. Cases of scarlet fever caused by group C organisms have been reported,[2b] suggesting that an erythrogenic toxin, similar to the erythrogenic toxin produced by streptococci of group A, is produced. Similar rashes have also been observed in cases of bacteremia caused by group G strains.[6] The relation between the erythrogenic toxins produced by the various groups has not been studied. The Schultz-Charlton test, using group A antiserum, might contribute valuable infor-

mation, but unfortunately it was not done in this case. Further similarities in the properties of organisms of groups A, C and G organisms are to be presented and discussed later in this paper.

### BACTERIOLOGIC DATA

The organisms were isolated from the patient's blood stream in dextrose infusion broth and on poured blood agar plates. On surface and on poured plates the colonies presented the typical appearance produced by organisms of Lancefield group C, which has been described by Rantz and Jewell.[13] Photographs of such plates are reproduced in figure 2. Surface and poured plates containing colonies of group A organisms are also included to show that their appearance differs from that of colonies of group C organisms. The chief difference lies in the size of the hemolytic zone, which is larger for group C strains and has a less distinct margin. The colony of group C organisms is somewhat larger, particularly on the poured plate.

The Lancefield grouping was performed by Rantz's modification of the formamide method of Fuller.[12a] The results were especially clearcut, more so than is usually observed with group C organisms, and there were no cross reactions.

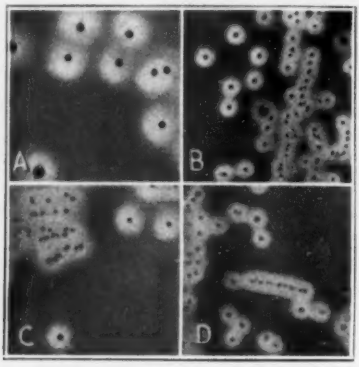


Fig. 2.—Poured (*A*) and surface (*C*) blood agar plates containing hemolytic streptococci of Lancefield group C isolated from our patient and similar preparations (*B*, poured plate; *D*, surface plate) of hemolytic streptococci of Lancefield group A. The colonies of group C organisms are larger than colonies of streptococci of group A, and the hemolytic zone is larger with a less distinct margin than that of the colonies of group A organisms.

After the organisms had been transferred in infusion broth daily for several weeks a small colony variant appeared. Its properties were studied but were not sufficiently different from the original large colony form to merit special mention.

### FIBRINOLYSIN

Tillett and Garner [14] found in 1933 that broth cultures and cell-free culture filtrates of many strains of hemolytic streptococci of human origin contain a substance capable of dissolving clots of normal human fibrin and that a resistance to this lytic action develops in the plasma of patients during or after infections caused

13. Rantz, L. A., and Jewell, M. L.: The Relationship of Serologic Groups A, B, and C of Lancefield to the Type of Hemolysis Produced by Streptococci in Poured Blood Agar Plates, J. Bact. **40**:1, 1940.

14. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**:485, 1933.

by hemolytic streptococci. Subsequent studies have shown that the test is not entirely specific for streptococcic infections, as increased amounts of antifibrinolysin have been noted in patients with gonococcic arthritis,[15] bacteremia caused by Streptococcus viridans [16] and pneumococcic pneumonia.[17]

Fibrinolysin is produced by streptococci belonging to group A, group C (human) and group G but not by organisms belonging to the other Lancefield groups.[18]

*Procedure and Results.*—The organisms isolated from our patient were transferred daily in broth culture, and antifibrinolysin tests were performed according to the method of Tillett and Garner,[14] except that the plasma-fibrinolysin solution was incubated for fifteen minutes before calcium chloride was added. Tests were

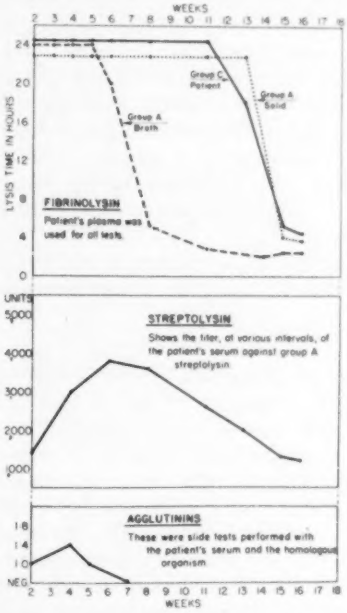


Fig. 3.—A summary of the immunologic data in the case reported here.

also made with solid fibrinolytic substance, prepared from a group A strain by the method of Garner and Tillett,[19] and with a broth culture of another group A strain.

15. Myers, W. K.; Keefer, C. S., and Holmes, W. F., Jr.: The Resistance to Fibrinolytic Activity of the Hemolytic Streptococcus with Special Reference to Patients with Rheumatic Fever and Rheumatoid (Atrophic) Arthritis, J. Clin. Investigation **14**:119, 1935.

16. Waaler, E.: Development of Antifibrinolytic Properties in Blood of Patients with Rheumatic Fever, Chronic Infective Arthritis, and Bacterial Endocarditis, J. Clin. Investigation **16**:145, 1937.

17. Boisvert, P. L.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940.

18. Tillett, W. S.: The Fibrinolytic Activity of Hemolytic Streptococci, Bact. Rev. **2**:161, 1938.

19. Garner, R. L., and Tillett, W. S.: Biochemical Studies on the Fibrinolytic Activity of Hemolytic Streptococci: I. Isolation and Characterization of Fibrinolysin, J. Exper. Med. **60**: 234, 1934.

The group C fibrinolysin was actively lytic, of almost the same potency as the solid group A substance. This similarity in action has been observed in over two hundred fibrinolysin tests. Comparative curves have been presented elsewhere.[20]

The patient's plasma was repeatedly tested against the fibrinolysin produced by the invading organism, as well as by the two group A strains. The results are presented in figure 3. Complete resistance to lysis developed for all three strains during the acute stage of the illness. The amount of antifibrinolysin began to decrease gradually after a few weeks, at different rates for each of the strains.

*Comment.*—There is a striking similarity in the action of the fibrinolysins produced by the group A and group C strains. Both are actively lytic and give almost identical results in normal persons and in persons with infections caused by organisms of group A. The titer of antifibrinolysin of the plasma of the patient with an infection caused by streptococci of group C is nearly the same when tested with group A and with group C lysins. If the fibrinolysins were group specific, there should have been a higher titer with the homologous than with the heterologous strains. As the titer fell, however, there was actually a shorter fibrinolysin time with the group C (homologous) strain. It was shown by Mote, Massell and Jones[21] that there are quantitative differences in the fibrinolysins and antifibrinolysins produced by various group A strains. The differences in the group A and group C described in this paper are of the same nature. However, if there were actual qualitative differences, the variations in titers should have been much wider than those recorded.

The evidence suggests that from a qualitative standpoint the fibrinolysins produced by group A and group C are similar, if not identical.

### STREPTOLYSIN

It has been known for many years that hemolytic streptococci produce a soluble substance which is capable of lysing red blood cells. This substance, called streptolysin, is antigenic[22]; i. e., when it is injected into the blood stream of animals, it stimulates the production of a substance, antistreptolysin, which will neutralize the hemolytic activity of streptolysin in vitro. Increased amounts of antistreptolysin in human beings also develop during or after infections caused by hemolytic streptococci. Determination of the titer of antistreptolysin has become an important method for the study of known streptococcic infections and also of diseases of obscure origin, such as rheumatic fever and glomerulonephritis, which are thought to be associated in some way with hemolytic streptococci.

The relation between the streptolysins produced by members of the various Lancefield groups is a subject of considerable interest. Todd[23] found that two distinct serologic varieties of streptolysin can be prepared from hemolytic streptococci of group A. They have been named streptolysin O, to indicate sensitivity to oxygen, and streptolysin S, to indicate extractability in serum. It was later shown,[24] by neutralization experiments with group A antistreptolysin O, that

20. Kirby, W. M. M., and Rantz, L. A.: The in Vitro and in Vivo Effect of Sulfonamides upon the Streptococcal Antifibrinolysin Test, J. Clin. Investigation **21**:295, 1942.

21. Mote, J. R.; Massell, B. F., and Jones, T. D.: Differences in Hemolytic Streptococcal Antifibrinolysins, J. Immunol. **36**:71, 1939.

22. Todd, E. W.: A Comparative Serological Study of Streptolysins Derived from Human and from Animal Infections, with Notes on Pneumococcal Hemolysin, Tetanolysin, and Staphylococcus Toxin, J. Path. & Bact. **39**:299, 1934.

23. Todd, E. W.: The Differentiation of Two Distinct Serological Varieties of Streptolysin, Streptolysin O and Streptolysin S, J. Path. & Bact. **47**:423, 1938.

24. Todd, E. W.: The Streptolysins of Various Groups and Types of Hemolytic Streptococci: A Serological Investigation, J. Hyg. **39**:1, 1939.

streptolysin O is formed by strains belonging to groups A, C (human) and G but not by strains belonging to groups B, C (animal), D, E, G and K. It was inferred that the streptolysins O produced by groups A, C and G were identical. This observation is of special interest when it is recalled that A, C and G are the three groups that most commonly cause infections in human beings.

Streptolysin S, on the other hand, is group specific[24]; i. e., group A antistreptolysin S does not neutralize the streptolysin S of any of the other groups.

The only description of titrations of antistreptolysin in human beings with infections caused by members of groups other than A is that of Longcope.[8] He found high titers of antistreptolysin O in 2 patients infected with the "minute hemolytic streptococci" of Long and Bliss,[9] which are members of group F. On the other hand, no streptolysin O was produced by the three group F strains studied by Todd,[24] so that the status of the members of this group needs to be further studied.

Since antistreptolysin has not been prepared by injection of group C streptolysin into animals, and since no previous studies have been reported on human subjects, it is of unusual interest to record the results of the experiments performed in connection with this patient.

*Comparison of Group A and Group C Streptolysin O*

| | Group A | Group C |
|---|---|---|
| Minimal hemolytic dose | | |
| Fresh culture | 0.05 cc. | 0.05 cc. |
| After filtration | 0.05 cc. | 0.05 cc. |
| After reduction | 0.05 cc. | 0.10 cc. |
| Combining unit with group A antistreptolysin | 0.25 cc. | 0.3 cc. |
| Titration with patient's serum on two occasions | 1,675 units<br>3,000 units | 2,500 units<br>3,000 units |

*Procedure and Results.*—Streptolysin O was prepared from group C organisms according to the method of Coburn and Pauli.[25] At the same time streptolysin O was made from a group A strain (Aronson-Schuetzer). The data concerning the two lysins is presented in the table. Their behavior was almost identical in all respects. The group A lysin produced hemolysis somewhat more rapidly, but no difference could be detected after one half-hour's incubation. Neutralization was clearcut, and the combining unit was readily determined with group A antistreptolysin. Of special interest were the titrations of the patient's serum with both group A and group C streptolysins. The patient's antistreptolysin titer against group A lysin is charted in figure 3, where it is correlated with the results of the agglutination and the fibrinolysin tests. A high titer developed early in the disease, and it was still considerably elevated at the time of the patient's death sixteen weeks later.

*Comment.*—The streptolysins O of groups A and C are much alike. They are both actively lytic and are readily neutralized by both group A and group C antistreptolysin. The group C lysin is antigenic and produced a high titer of antistreptolysin in the patient's serum. The titer was the same with group A and group C streptolysins, which suggests that no group specificity exists, but that the streptolysins produced by the two groups are similar if not identical.

25. Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process: I. The Determination of Antistreptolysin Titer, J. Exper. Med. **62**:129, 1935.